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(54) Title: SYNTHESIS OF TAXOL AND ITS DERIVATIVES

(57) Abstract

Process for the synthesis of taxol and other tricyclic and tetracyclic taxanes.

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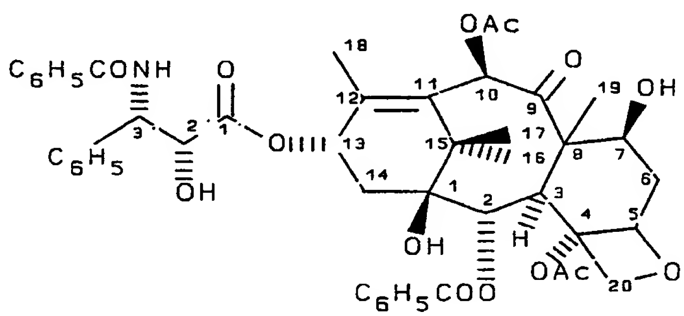
Synthesis of Taxol and its derivatives.

This invention was made with Government support under NIH Grant #CA 42031 awarded by the National Institites of Health. The United States Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

The present invention is directed to a process for the synthesis of taxol and other tricyclic and tetracyclic taxanes and novel intermediates thereof.

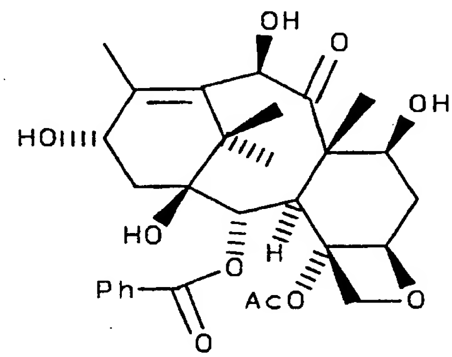
The taxane family of terpenes, of which taxol is a member, has attracted considerable interest in both the biological and chemical arts. Taxol is a promising cancer chemotherapeutic agent with a broad spectrum of antileukemic and tumor-inhibiting activity. Taxol has the following structure:



wherein Ac is acetyl.

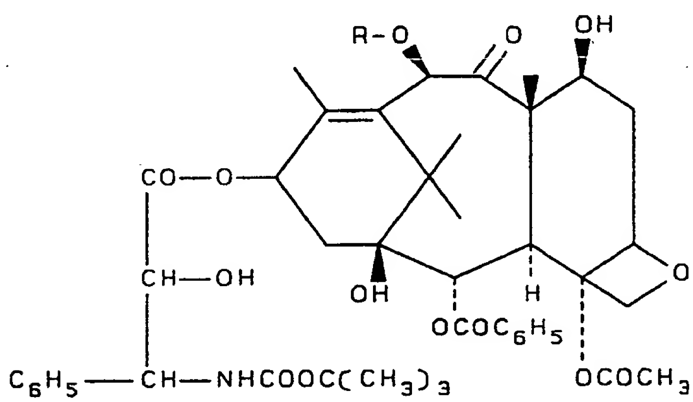
The supply of taxol is presently being provided by the bark from Taxus brevifollia (Western Yew). However, taxol is found only in minute quantities in the bark of these slow growing evergreens. Consequently, chemists in recent years have expended their energies in trying to find a viable synthetic route for the preparation of taxol. To date, the results have not been entirely satisfactory.

A semi-synthetic approach to the preparation of taxol has been described by Greene, et al. in JACS 110, 5917 (1988), and involves the use of a congener of taxol, 10-deacetyl baccatin III which has the structure of formula II shown below:



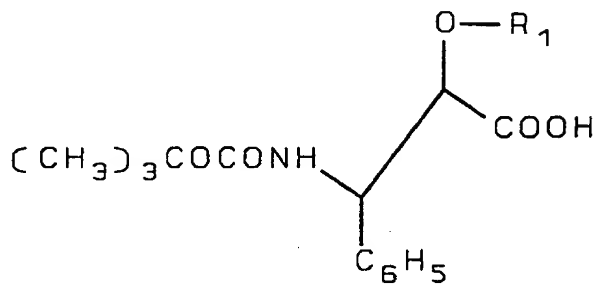
10-deacetyl baccatin III is more readily available than taxol since it can be obtained from the needles of Taxus baccata. According to the method of Greene et al., 10-deacetyl baccatin III ("10-DAB") is converted to taxol by attachment of the C-10 acetyl group and by attachment of the C-13 ß-amido ester side chain through the esterification of the C-13 alcohol with a ß-amido carboxylic acid unit.

Denis ét al. in U.S. Patent No. 4,924,011 disclose another process for preparing derivatives of baccatin III or of 10-deactylbaccatin III of general formula

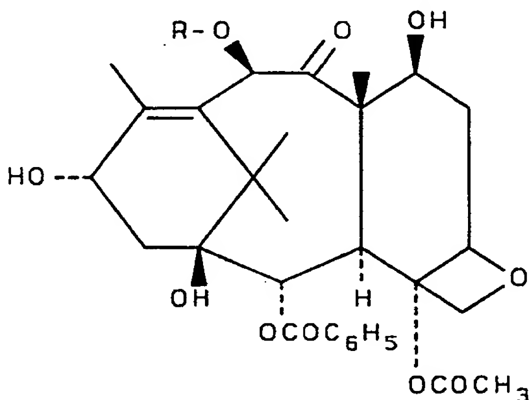


(V)

in which R′ denotes hydrogen or acetyl. As reported, an acid of general formula:



in which R_1 is a hydroxy-protecting group, is condensed with a taxane derivative of general formula:



(VII)

in which R_2 is an acetyl hydroxy-protecting group and R_3 is a hydroxy-protecting group, and the protecting groups R_1, R_3 and, where appropriate, R_2 are then replaced by hydrogen.

Other semisynthetic approaches for the preparation of taxol and for the preparation of other taxanes which possess tumor-inhibiting properties have been reported in recent years, but each of these approaches requires 10-DAB or baccatin III as a starting material. As such, the supply of taxol and other taxane derivatives remains dependent at least to some extent upon the collection of various parts of plants from the

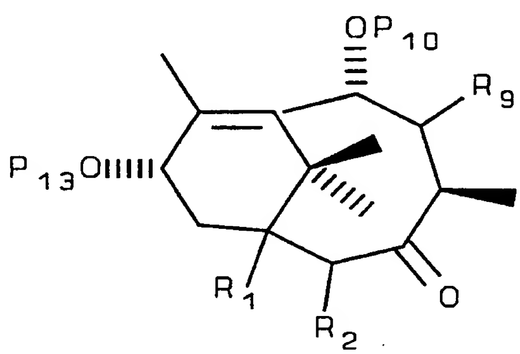
remote corners of the world and the extraction of 10-DAB and/or baccatin III therefrom.

SUMMARY OF THE INVENTION

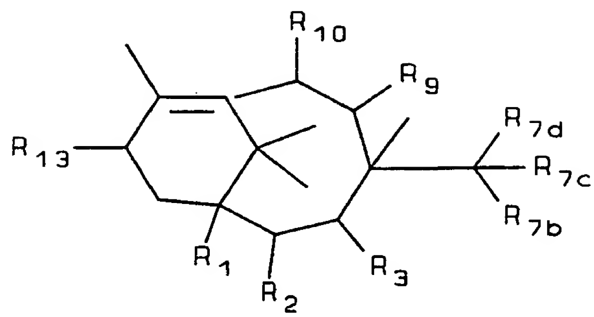
Among the objects of the present invention, therefore, is the provision of a process for the synthesis of taxol and other tetracyclic taxanes; the provision of such a process which is highly diastereoselective; the provision of such a process which proceeds in relatively high yield; and the provision of key intermediates and processes for their preparation.

Briefly, therefore, the present invention is directed to a process for the preparation of taxol and other tricyclic and tetracyclic taxanes.

In accordance with one aspect of the present invention, the process comprises reacting a compound having the formula



with $BrMgN(iPr)_2$, an aldehyde (or ketone), followed by phosgene and an alcohol to form a compound having the formula:



wherein

R_1 is hydrogen or protected hydroxy; R_2 is hydrogen or protected hydroxy;

R_3 is oxo;

R_{7b} is hydrogen, alkyl, cyano, hydroxy, protected hydroxy, or $-OCOR_{36}$, or together with R_3 or R_9 is a carbonate;

R_{7c} and R_{7d} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl;

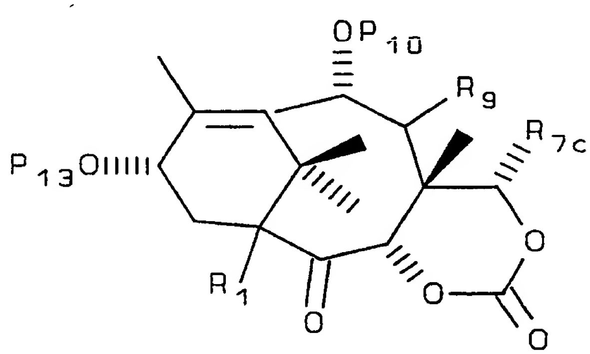
R_9 is hydrogen, protected hydroxy, or oxo;

R_{10} is $-OP_{10}$;

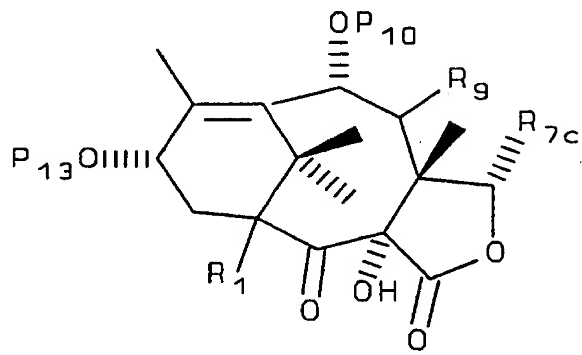
R_{13} is $-OP_{13}$; and

P_{10} and P_{13} are hydroxy protecting groups.

In accordance with another aspect of the present invention, the process comprises reacting a compound having the formula



with lithium tetramethylpiperidide to form a compound having the formula:



;

wherein

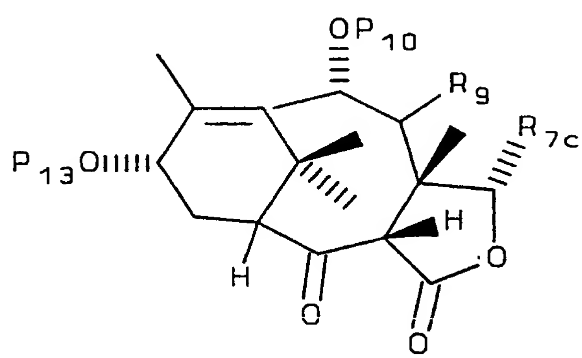
R_1 is hydrogen or protected hydroxy;

R_{7c} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl;

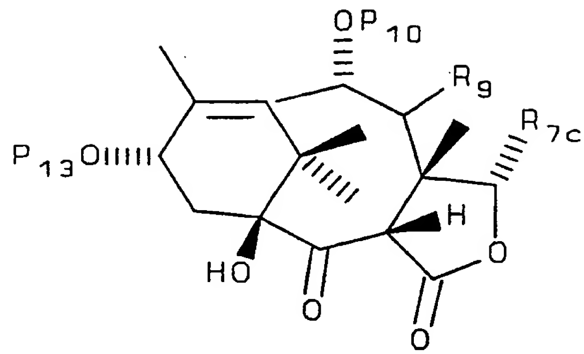
R_9 is hydrogen, protected hydroxy, or oxo; and

P_{10} and P_{13} are hydroxy protecting groups.

In accordance with another aspect of the present invention, the process comprises reacting a compound having the formula:



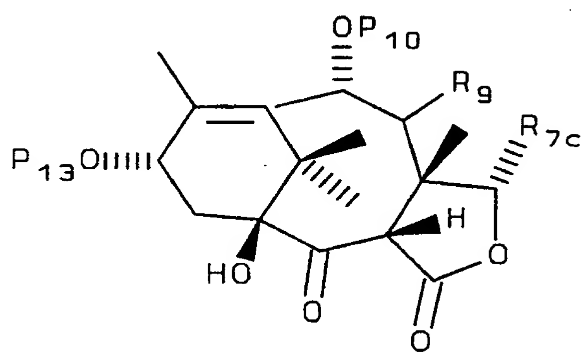
with lithium tetramethylpiperidide and camphosulfonyl oxaziridine to form a compound having the formula:



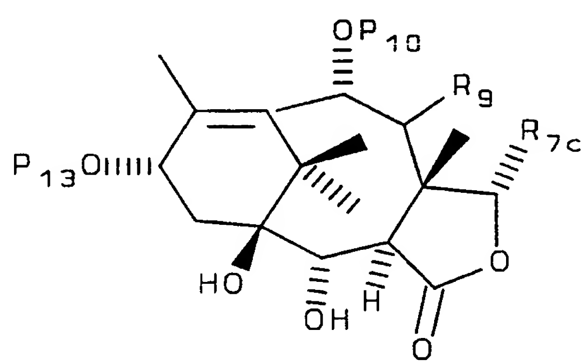
;

wherein R_9 is hydrogen, protected hydroxy, or oxo; R_{7c} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl; and P_{10} and P_{13} are hydroxy protecting groups.

In accordance with another aspect of the present invention, the process comprises reacting a compound having the formula:



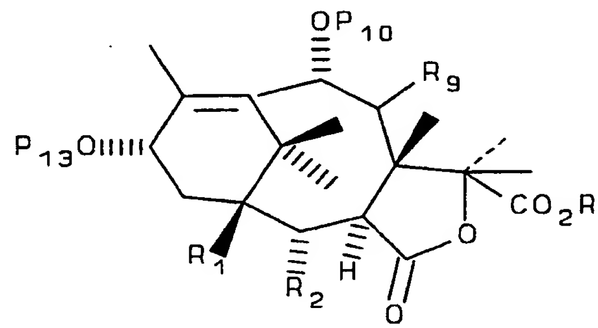
with a hydride reducing agent, preferably Red-Al, to form a compound having the formula:



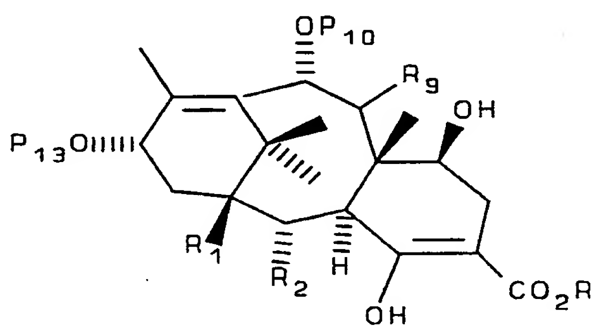
;

wherein R_9 is hydrogen, protected hydroxy, or oxo; R_{7c} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl; and P_{10} and P_{13} are hydroxy protecting groups.

In accordance with another aspect of the present invention, the process comprises reacting a compound having the formula:



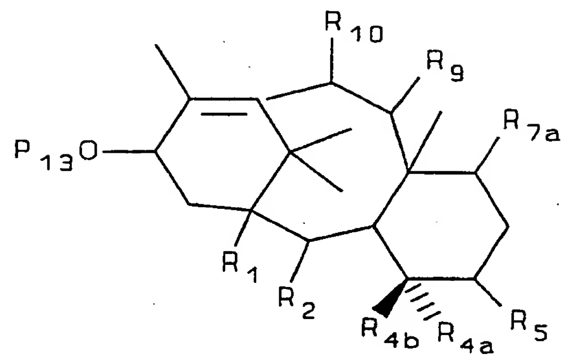
with lithium diisopropylamide to form a compound having the formula:



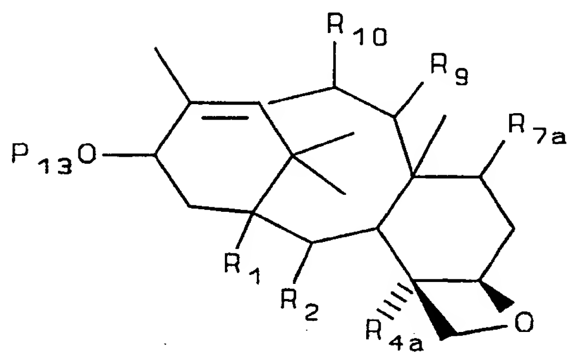
;

wherein R is lower alkyl, R_1 is hydrogen, protected hydroxy or R_1 and R_2 together form a carbonate, R_2 is hydrogen, protected hydroxy or R_1 and R_2 together form a carbonate, R_9 is hydrogen, protected hydroxy, or oxo; R_{7c} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl; and P_{10} and P_{13} are hydroxy protecting groups.

In accordance with another aspect of the present invention, the process comprises reacting a compound having the formula:



with DBU to form a compound having the formula:



wherein

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, or together with R_1 is a carbonate;

R_{4a} is hydrogen, alkyl, hydroxy, or protected hydroxy, or together with R_2 is a carbonate;

R_{4b} is hydroxymethylene;

R_5 is -OMs, -OTs or a bromide;

R_{7a} is hydrogen, protected hydroxy, or $-OCOR_{34}$, or together with R_9 is a carbonate;

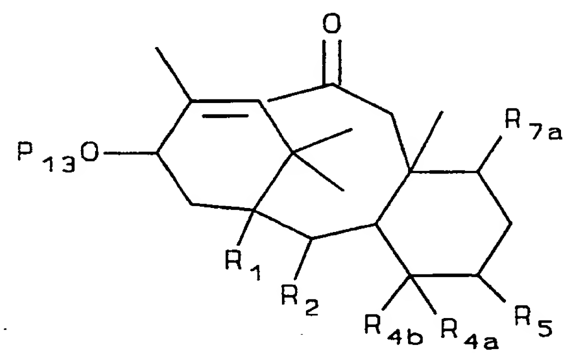
R_9 is hydrogen, oxo, hydroxy, protected hydroxy, or $-OCOR_{33}$, or together with R_{7a} or R_{10} is a carbonate;

R_{10} is hydrogen, oxo, hydroxy, protected hydroxy, or $-OCOR_{29}$, or together with R_9 is a carbonate;

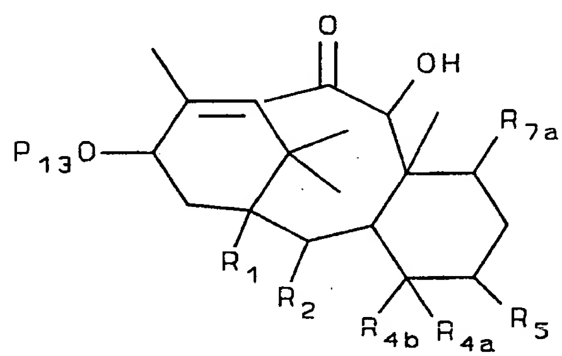
R_{13} is hydrogen, hydroxy, protected hydroxy, or $-OCOR_{35}$;

R_{29}, R_{33}, R_{34} and R_{35} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

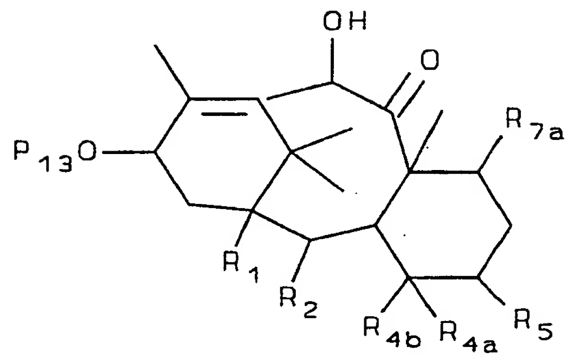
In accordance with another aspect of the present invention, the process comprises reacting a compound having the formula:



with KOtBu and $(PhSeO)_2O$ to form a compound having the formula:



which rearranges in the presence of additional KOtBu, silica gel, or other acids or bases, or with heat to a compound having the formula:



wherein

R_1 is hydrogen, hydroxy, protected hydroxy, or together with R_2 is a carbonate;

R_2 is hydrogen, protected hydroxy, or $-OCOR_{31}$, or together with R_1 or R_{4a} is a carbonate;

R_{4a} is hydrogen, alkyl, hydroxy, protected hydroxy, or $-OCOR_{27}$, together with R_{4b} is an oxo, or together with R_2, R_{4b}, or R_5 is a carbonate;

R_{4b} is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or cyano, together with R_{4a} is an oxo, together with R_{4a} or R_5 is a carbonate, or together with R_5 and the carbons to which they are attached form an oxetane ring;

R_5 is hydrogen, protected hydroxy, $-OCOR_{37}$, together with R_{4a} or R_{4b} is a carbonate, or together with R_{4b} and the carbons to which they are attached form an oxetane ring;

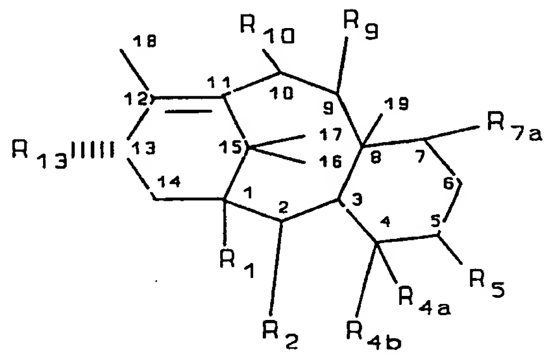
R_{7a} is hydrogen, halogen, protected hydroxy, or $-OCOR_{34}$; and

R_{27}, R_{29}, R_{30}, R_{31}, R_{33}, R_{34}, R_{35} and R_{37} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl.

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_{10} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterosubstituted alkyl, alkenyl alkynyl, aryl or heteroaryl;

In general, the process of the present invention may be used to prepare taxanes having the formula:



(1)

wherein

R_1 is hydrogen, hydroxy, protected hydroxy, or $-OCOR_{30}$;

R_2 is hydrogen, hydroxy, $-OCOR_{31}$, or oxo;

R_{4a} is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cyano, hydroxy, $-OCOR_{27}$, or together with R_{4b} forms an oxo, oxirane or methylene;

R_{4b} is hydrogen, together with R_{4a} forms an oxo, oxirane or methylene, or together with R_5 and the carbon atoms to which they are attached form an oxetane ring;

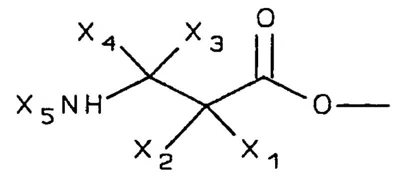
R_5 is hydrogen, halogen, hydroxy, protected hydroxy, $-OCOR_{37}$, oxo, or together with R_{4b} and the carbon atoms to which they are attached form an oxetane ring;

R_{7a} is hydrogen, halogen, hydroxy, protected hydroxy, $-OCOR_{34}$, oxo, or $-OR_{28}$;

R_9 is hydrogen, hydroxy, protected hydroxy, acyloxy, or oxo;

R_{10} is hydrogen, $-OCOR_{29}$, hydroxy, protected hydroxy, or oxo;

R_{13} is hydroxy, protected hydroxy, MO- or



;

R_{28} is a functional group which increases the solubility of the taxane;

R_{27}, R_{29}, R_{30}, R_{31}, R_{34} and R_{37} are independently hydrogen, alkyl, alkenyl, alkynyl, monocyclic aryl or monocyclic heteroaryl;

X_1 is $-OX_6$, $-SX_7$, or $-NX_8X_9$;

X_2 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_3 and X_4 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_5 is $-COX_{10}$, $-COOX_{10}$, $-COSX_{10}$, $-CONX_8X_{10}$, or $-SO_2X_{11}$;

X_6 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, hydroxy protecting group, or a functional group which increases the water solubility of the taxane derivative;

X_7 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or sulfhydryl protecting group;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_9 is an amino protecting group;

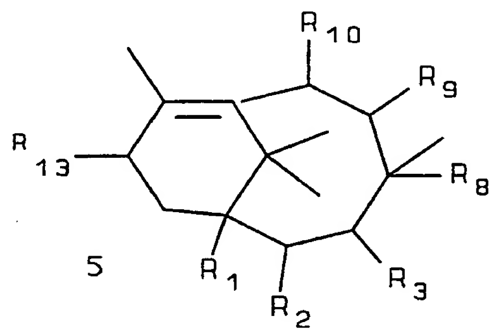
X_{10} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterosubstituted alkyl, alkenyl alkynyl, aryl or heteroaryl;

X_{11} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-OX_{10}$, or $-NX_8X_{14}$;

X_{14} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

M comprises ammonium or is a metal.

The present invention is additionally directed to an intermediate for use in the preparation of a tricyclic or tetracyclic taxane having the formula:



wherein

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, or together with R_1 is a carbonate;

R_3 is hydrogen, hydroxy, protected hydroxy, $-OCOR_{32}$, or oxo;

R_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl;

R_9 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{33}$, or together with R_{10} is a carbonate;

R_{10} is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{29}$, or together with R_9 is a carbonate;

R_{13} is hydrogen, hydroxy, protected hydroxy, $-OCOR_{35}$ or MO-;

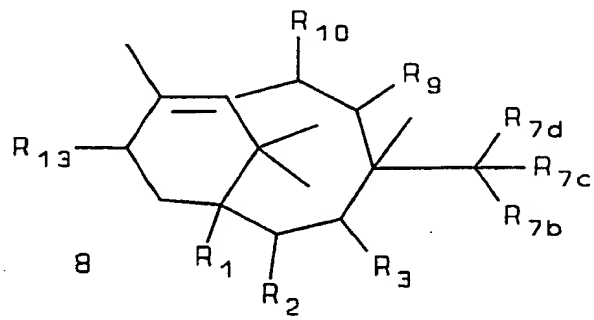
R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, and R_{35} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

M comprises ammonium or is a metal.

The present invention is further directed to an intermediate for use in the preparation of a tricyclic or tetracyclic taxane having the formula:



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wherein

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, or together with R_1 is a carbonate;

R_3 is hydrogen, hydroxy, protected hydroxy, $-OCOR_{32}$, or oxo, or together with R_{7b} is a carbonate;

R_{7b} is hydrogen, alkyl, cyano, hydroxy, protected hydroxy, or $-OCOR_{36}$, or together with R_3 or R_9 is a carbonate;

R_{7c} and R_{7d} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl;

R_9 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{33}$, or together with R_{7b} or R_{10} is a carbonate;

R_{10} is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{29}$, or together with R_9 is a carbonate;

R_{13} is hydrogen, hydroxy, protected hydroxy, $-OCOR_{35}$ or MO-;

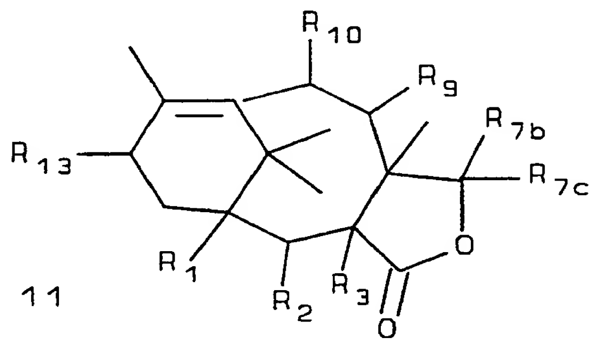
R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{35} and R_{36} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

M comprises ammonium or is a metal.

The invention is further directed to an intermediate for use in the preparation of a tricyclic or tetracyclic taxane having the formula:



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wherein

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, or together with R_1 is a carbonate;

R_3 is hydrogen, hydroxy, protected hydroxy, or $-OCOR_{32}$;

R_{7b} is hydrogen, alkyl, cyano, hydroxy, protected hydroxy, or $-OCOR_{36}$, or together with R_3 or R_9 is a carbonate;

R_{7c} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl;

R_9 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{33}$, or together with R_{10} is a carbonate;

R_{10} is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{29}$, or together with R_9 is a carbonate;

R_{13} is hydrogen, hydroxy, protected hydroxy, $-OCOR_{35}$ or MO-;

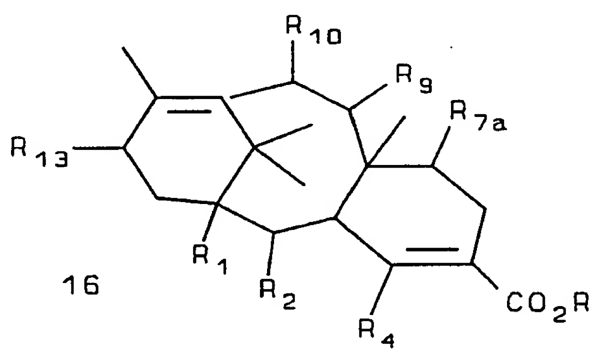
R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, and R_{35} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

M comprises ammonium or is a metal.

The present invention is further directed to an intermediate for use in the preparation of a tricyclic or tetracyclic taxane having the formula:



16

wherein

R is C_1 - C_8 alkyl,

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, together with R_1 is a carbonate, or together with R_4 is a carbonate;

R_{4a} is hydrogen, alkyl, hydroxy, protected hydroxy, or $-OCOR_{27}$, or together with R_2 is a carbonate;

R_{7a} is hydrogen, halogen, hydroxy, protected hydroxy, $-OCOR_{34}$, or together with R_9 is a carbonate;

R_9 is hydrogen, oxo, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{33}$, or together with R_{7a} or R_{10} is a carbonate;

R_{10} is hydrogen, oxo, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{29}$, or together with R_9 is a carbonate;

R_{13} is hydrogen, hydroxy, protected hydroxy, $-OCOR_{35}$ or MO-;

R_{28} is a functional group which increases the solubility of the taxane derivative;

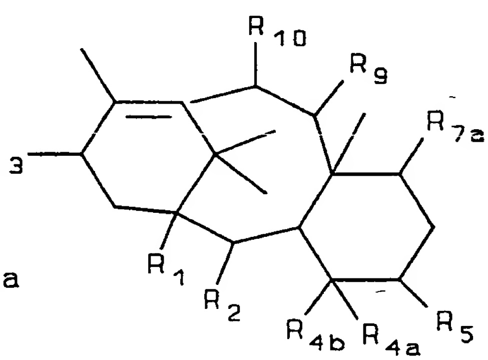
R_{27}, R_{29}, R_{30}, R_{31}, R_{33}, R_{34}, and R_{35} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

M comprises ammonium or is a metal.

The invention is further directed to an intermediate for use in the preparation of a tricyclic or tetracyclic taxane having the formula:



26a

wherein

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, or together with R_1 or R_{4a} is a carbonate;

R_{4a} is hydrogen, alkyl, hydroxy, protected hydroxy, or $-OCOR_{27}$, together with R_{4b} is an oxo, or together with R_2, R_{4b}, or R_5 is a carbonate;

R_{4b} is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or cyano, together with R_{4a} is an oxo, together with R_{4a} or R_5 is a carbonate, or together with R_5 and the carbons to which they are attached form an oxetane ring;

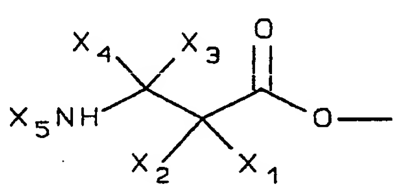
R_5 is hydrogen, hydroxy, protected hydroxy, -OCOR__, oxo, together with R_{4a} or R_{4b} is a carbonate, or together with R_{4b} and the carbons to which they are attached form an oxetane ring;

R_{7a} is hydrogen, halogen, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{34}$, or together with R_9 is a carbonate;

R_9 is hydrogen, oxo, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{33}$, or together with R_{7a} or R_{10} is a carbonate;

R_{10} is hydrogen, oxo, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{29}$, or together with R_9 is a carbonate;

R_{13} is hydrogen, hydroxy, protected hydroxy, $-OCOR_{35}$, MO- or



;

R_{28} is a functional group which increases the solubility of the taxane derivative;

R_{27}, R_{29}, R_{30}, R_{31}, R_{33}, and R_{35} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_1 is $-OX_6$, $-SX_7$, or $-NX_8X_9$;

X_2 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_3 and X_4 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_5 is $-COX_{10}$, $-COOX_{10}$, $-COSX_{10}$, $-CONX_8X_{10}$, or $-SO_2X_{11}$;

X_6 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, hydroxy protecting group, or a functional group which increases the water solubility of the taxane derivative;

X_7 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or sulfhydryl protecting group;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_9 is an amino protecting group;

X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_{11} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-OX_{10}$, or $-NX_8X_{14}$;

X_{14} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

M comprises ammonium or is a metal.

Other objects and features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As used herein "Ar" means aryl; "Ph" means phenyl; "Me" means methyl; "Et" means ethyl; "iPr" means isopropyl; "tBu" and "t-Bu" means tert-butyl; "R" means lower alkyl unless otherwise defined; "Ac" means acetyl; "py" means pyridine; "TES" means triethylsilyl; "TMS"

means trimethyl-silyl; "TBS" means Me_2t-BuSi-; "Tf" means $-SO_2CF_3$; "BMDA" means $BrMgNiPr_2$; "Swern" means $(COCl)_2$, Et_3N; "LTMP" means lithium tetramethylpiperidide; "MOP" means 2-methoxy-2-propyl; "BOM" means benzyloxymethyl; "LDA" means lithium diisopropylamide; "LAH" means lithium aluminum hydride; "Red-Al" means sodium bis(2-methoxyethoxy) aluminum hydride; "Ms" means CH_3SO_2-; "TASF" means tris(diethylamino)sulfonium-difluorotrimethylsilicate; "Ts" means toluenesulfonyl; "TBAF" means tetrabutyl ammonium hydride; "TPAP" means tetrapropyl-ammonium perruthenate; "DBU" means diazabicycloundecane; "DMAP" means p-dimethylamino pyridine; "LHMDS" means lithium hexamethyldisilazide; "DMF" means dimethylformamide; "AIBN" means azo-(bis)-isobutyronitrile; "10-DAB" means 10-desacetylbaccatin III; "FAR" means 2-chloro-1,1,2-trifluorotriethylamine; "mCPBA" means metachloroperbenzoic acid; "DDQ" means dicyanodichloroquinone; "sulfhydryl protecting group" includes, but is not limited to, hemithioacetals such as 1-ethoxyethyl and methoxymethyl, thioesters, or thiocarbonates; "amine protecting group" includes, but is not limited to, carbamates, for example, 2,2,2-trichloroethylcarbamate or tertbutylcarbamate; "protected hydroxy" means -OP wherein P is a hydroxy protecting group; and "hydroxy protecting group" includes, but is not limited to, acetals having two to ten carbons, ketals having two to ten carbons, ethers such as methyl, t-butyl, benzyl, p-methoxybenzyl, p-nitrobenzyl, allyl, trityl, methoxymethyl, methoxyethoxymethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrothiopyranyl, and trialkylsilyl ethers such as trimethylsilyl ether, triethylsilyl ether, dimethylarylsilyl ether, triisopropylsilyl ether and t-butyldimethylsilyl ether; esters such as benzoyl, acetyl, phenylacetyl, formyl, mono-, di-, and trihaloacetyl such as chloroacetyl, dichloroacetyl,

trichloroacetyl, trifluoro-acetyl; and carbonates including but not limited to alkyl carbonates having from one to six carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl; isobutyl, and n-pentyl; alkyl carbonates having from one to six carbon atoms and substituted with one or more halogen atoms such as 2,2,2-trichloroethoxymethyl and 2,2,2-tri-chloroethyl; alkenyl carbonates having from two to six carbon atoms such as vinyl and allyl; cycloalkyl carbonates having from three to six carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; and phenyl or benzyl carbonates optionally substituted on the ring with one or more C_{1-6} alkoxy, or nitro. Other hydroxyl, sulfhydryl and amine protecting groups may be found in "Protective Groups in Organic Synthesis" by T. W. Greene, John Wiley and Sons, 1981.

The alkyl groups described herein are preferably lower alkyl containing from one to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include methyl, ethyl, propyl, isopropyl, butyl, hexyl and the like. They may be hydrocarbon or heterosubstituted with the various substituents defined herein, including heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, aryl, heteroaryl, and heterosubstituted heteroaryl.

The alkenyl groups described herein are preferably lower alkenyl containing from two to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, and the like. They may be hydrocarbon or heterosubstituted with the various substituents defined herein, including alkyl, heteroalkyl, heteroalkenyl, alkynyl, heteroalkynyl, aryl, heteroaryl, and heterosubstituted heteroaryl.

The alkynyl groups described herein are preferably lower alkynyl containing from two to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, hexynyl, and the like. They may be hydrocarbon or heterosubstituted with the various substituents defined herein, including alkyl, heteroalkyl, alkenyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, and heterosubstituted heteroaryl.

The aryl moieties described herein contain from 6 to 15 carbon atoms and include phenyl. They may be hydro-carbon or heterosubstituted with the various substituents defined herein, including alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, heteroaryl, and heterosubstituted heteroaryl. Phenyl is the more preferred aryl.

The heteroaryl moieties described herein contain from 5 to 15 atoms and include, furyl, thienyl, pyridyl and the like. They may be hydrocarbon or heterosubstituted with the various substituents defined herein, including alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, aryl, and heterosubstituted heteroaryl.

The acyl moieties described herein contain alkyl, alkenyl, alkynyl, aryl or heteroaryl groups.

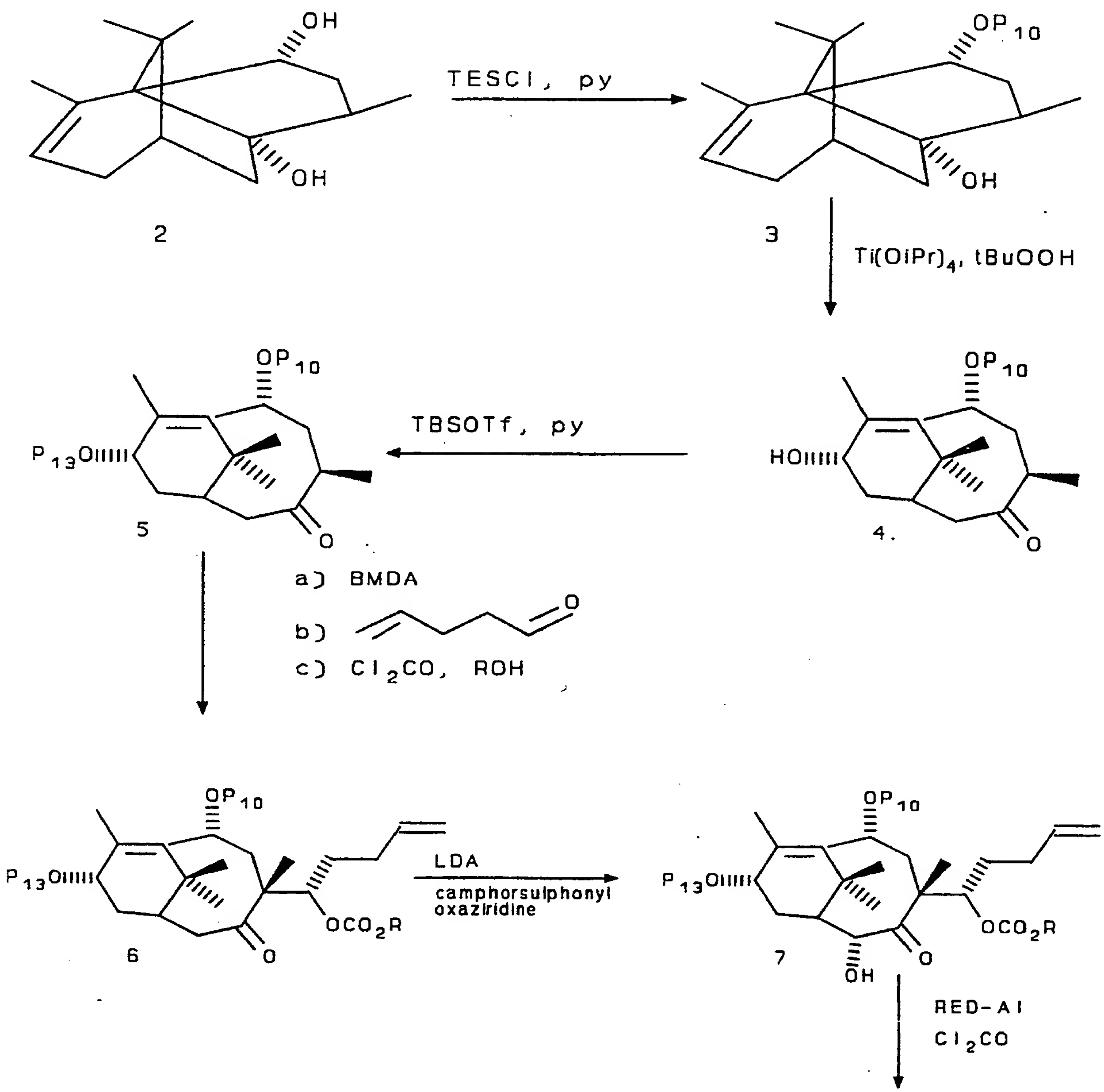
The alkoxycarbonyloxy moieties described herein comprise lower alkyl, alkenyl, alkynyl or aryl groups.

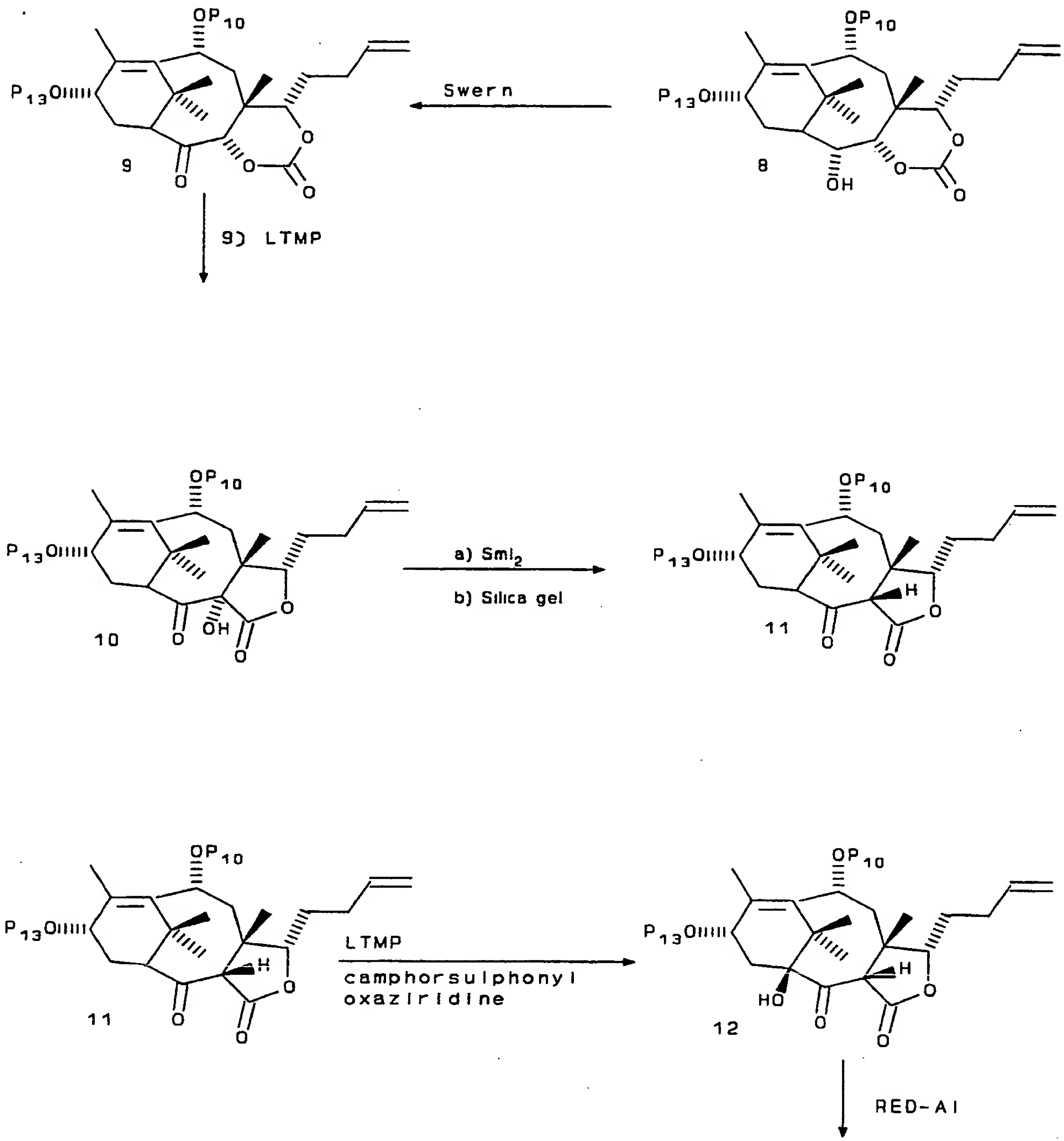
The hydrocarbon substituents described herein may be alkyl, alkenyl, alkynyl, or aryl, and the hetero-substituents of the heterosubstituted alkyl, alkenyl, alkynyl, aryl, and heteroaryl moieties described herein contain nitrogen, oxygen, sulfur, halogens and/or one to six carbons, and include lower alkoxy such as methoxy, ethoxy, butoxy, halogen such as chloro or fluoro, and nitro, heteroaryl such as furyl or thienyl, alkanoxy,

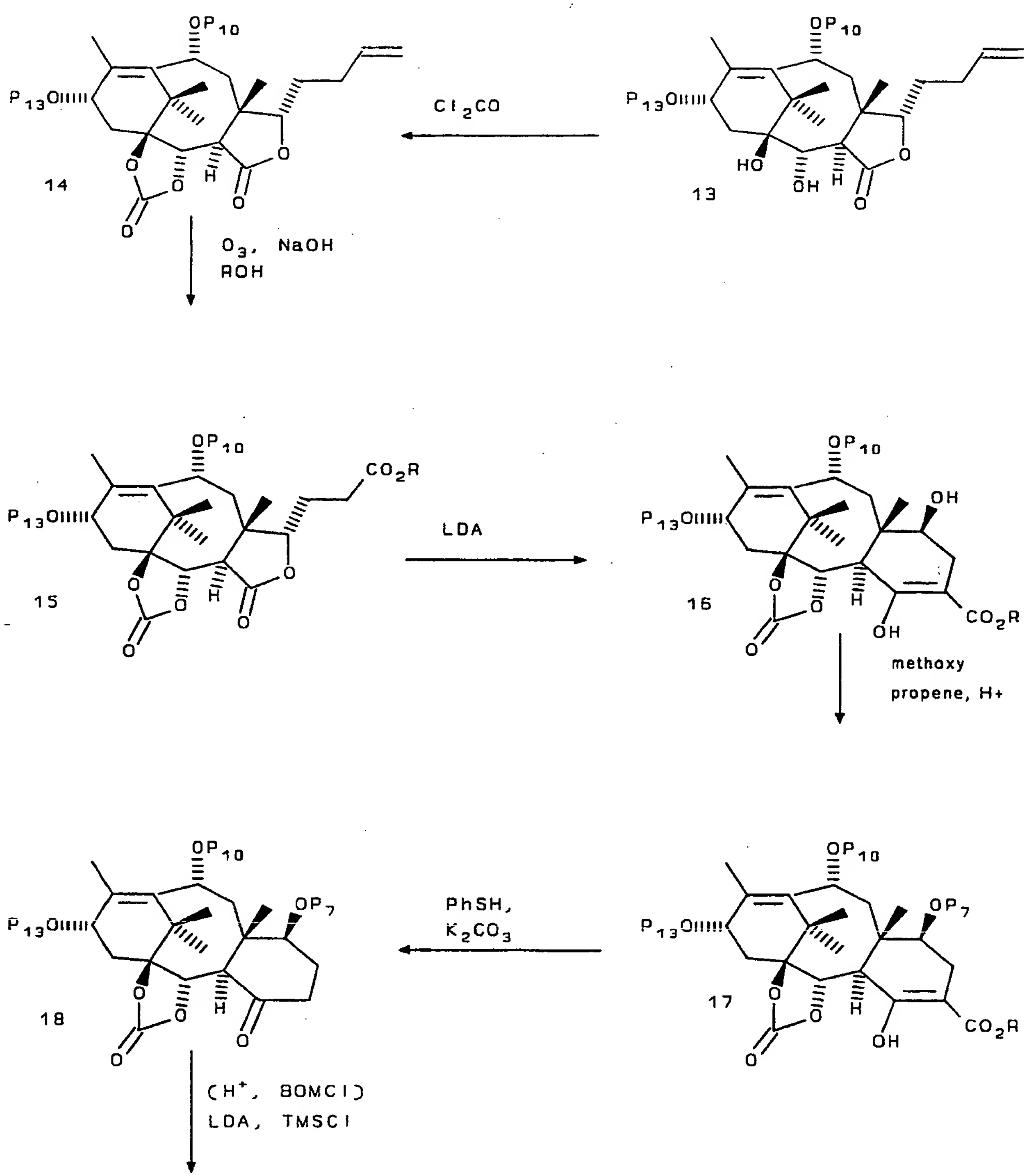
hydroxy, protected hydroxy, acyl, acyloxy, nitro, amino, and amido.

An exemplary synthesis of baccatin III or 10-DAB is depicted hereinbelow in Reaction Scheme A. The starting material, diol **2**, can be prepared from patchino (commonly known as B-patchouline epoxide) which is commercially available. The patchino is first reacted with an organo-metallic, such as lithium t-butyl followed by oxidation with an organic peroxide, such as t-butylperoxide in the presence of titanium tetraisopropoxide to form a tertiary alcohol. The tertiary alcohol is then reacted with a Lewis acid, such as boron trifluoride at low temperature, in the range from 40°C to -100°C; in the presence of an acid, such as trifluoromethane sulfonic acid. A graphical depiction of this reaction scheme along with an experimental write-up for the preparation of diol **2** can be found in U.S. Patent No. 4,876,399.

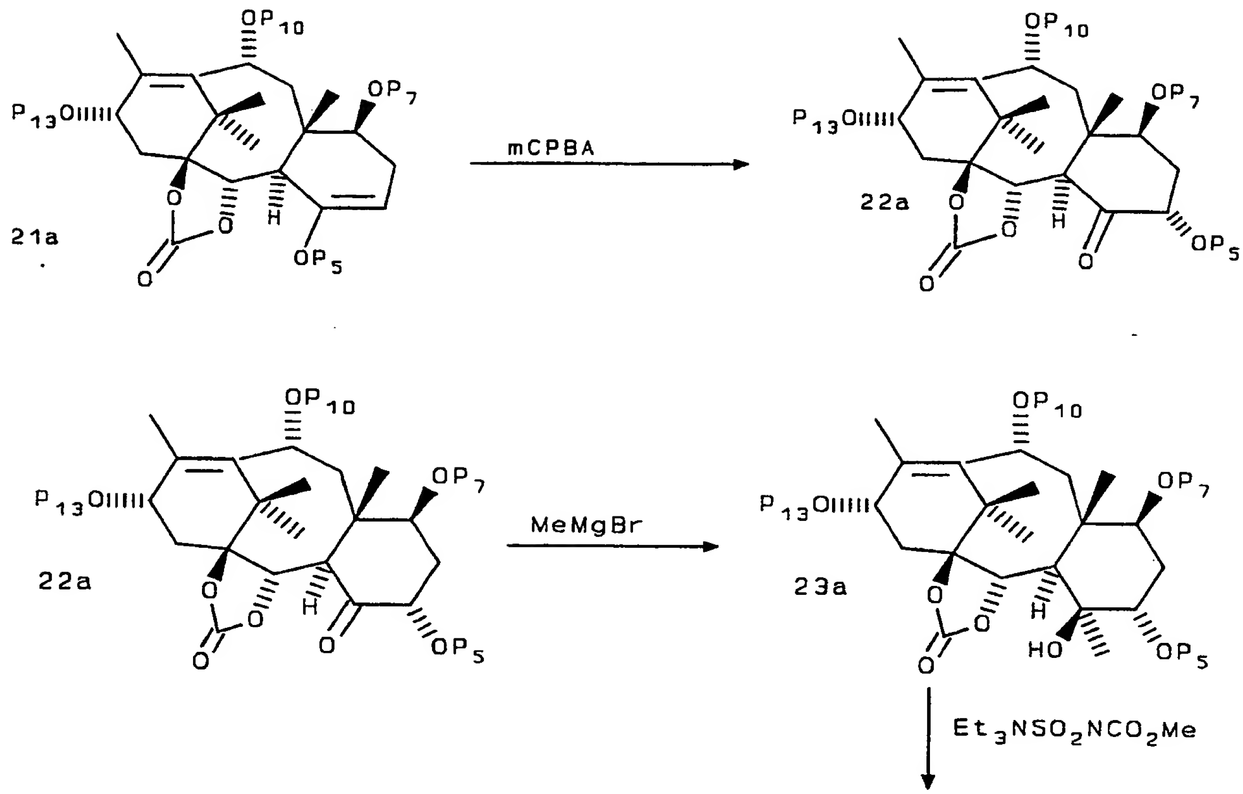
Reaction Scheme A

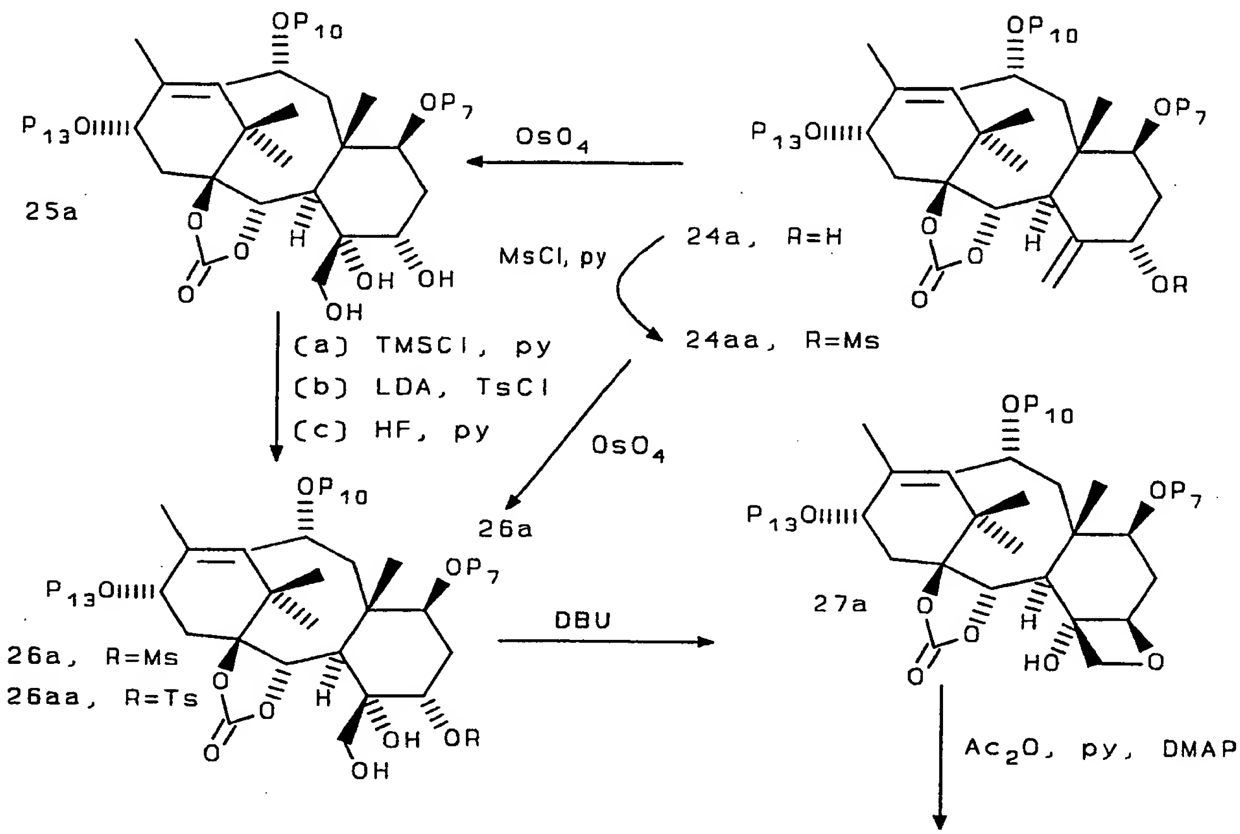


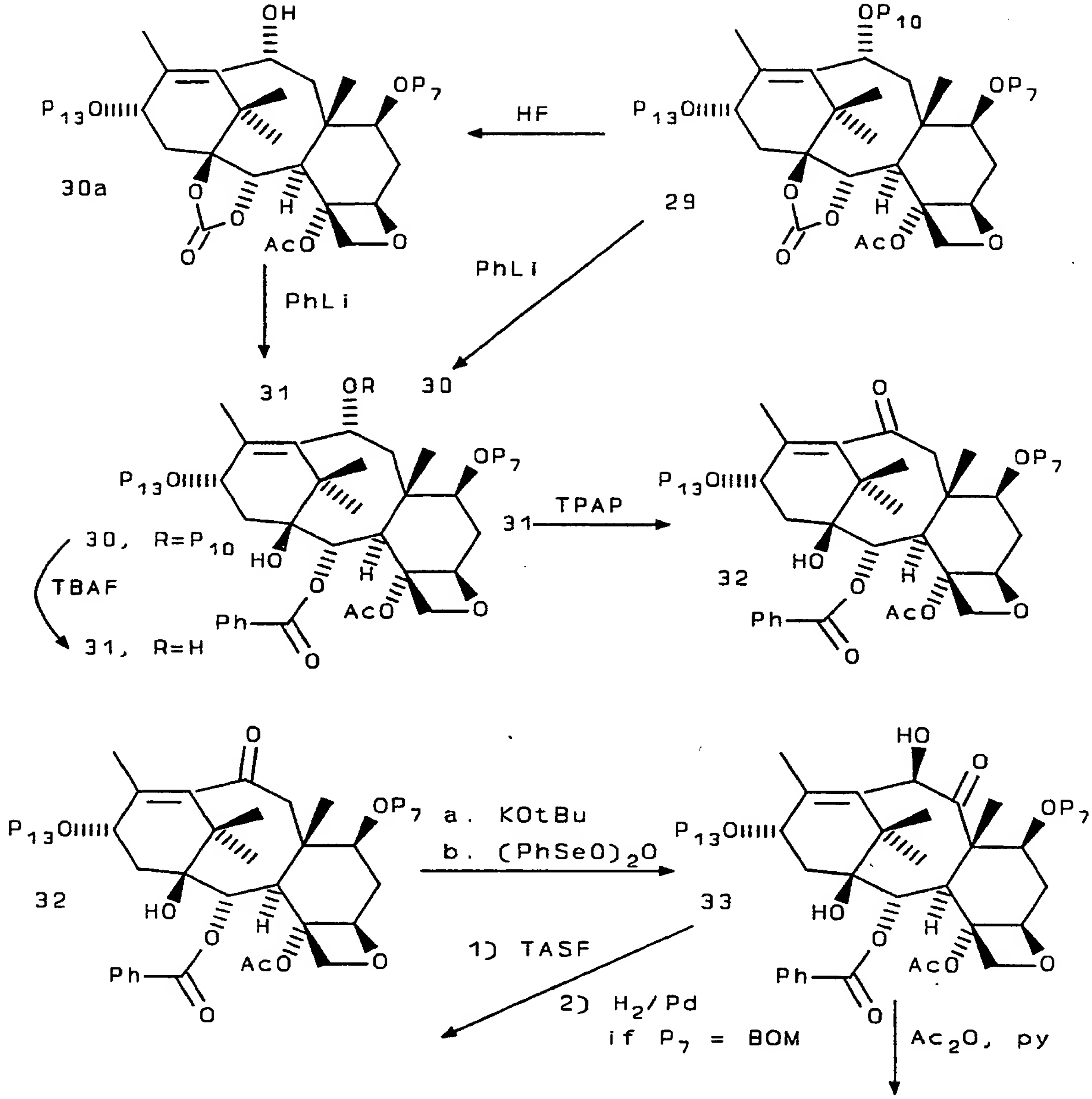

Swern
9) LTMP
a) SmI_2
b) Silica gel
LTMP
camphorsulphonyl oxaziridine
RED-Al
9
8
10
11
11
12

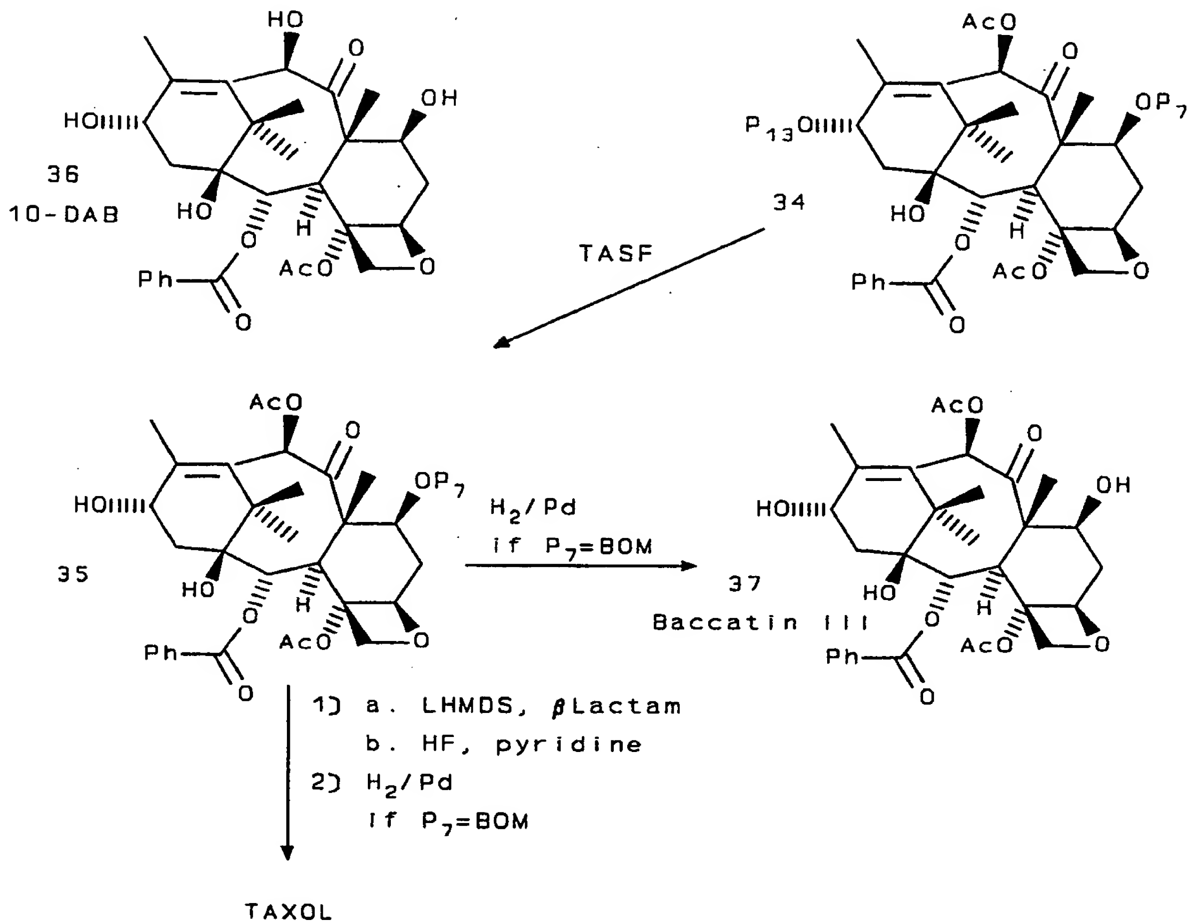


13
14
15
16
17
18
Cl2CO
O3, NaOH
ROH
LDA
methoxy
propene, H+
PhSH,
K2CO3
(H+, BOMCl)
LDA, TMSCl


21a
mCPBA
22a
22a
MeMgBr
23a
Et3NSO2NCO2Me


OP10
OP7
P13O
25a
O
O
O
H
OH OH
OH
OsO4
24a, R=H
MsCl, py
24aa, R=Ms
OR
(a) TMSCl, py
(b) LDA, TsCl
(c) HF, py
OsO4
26a
26a, R=Ms
26aa, R=Ts
DBU
27a
HO
Ac2O, py, DMAP

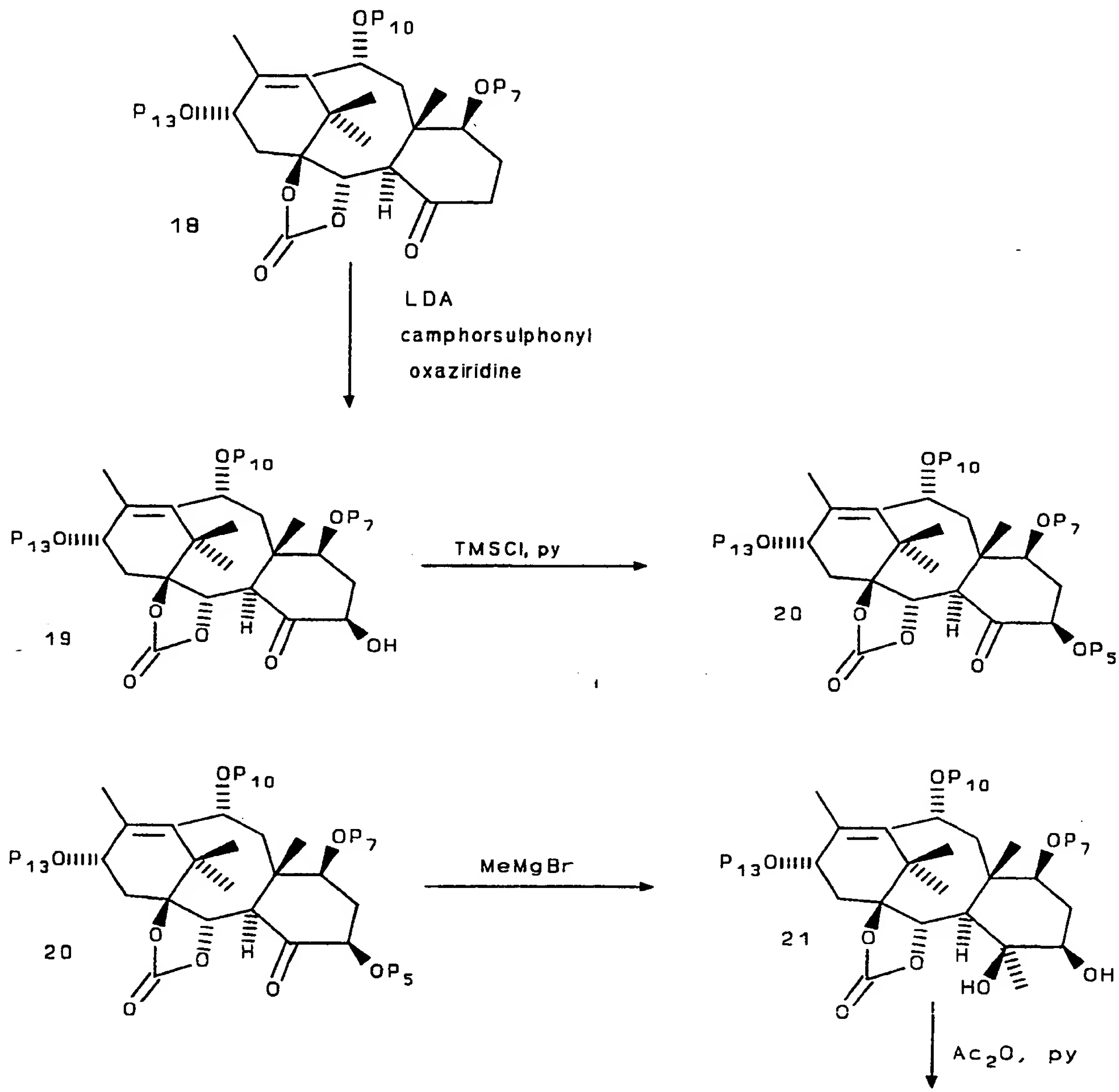

HF
29
30a
PhLi
PhLi
31
30
30, R=P10
TBAF
31, R=H
31
TPAP
32
32
a. KOtBu
b. (PhSeO)2O
33
1) TASF
2) H2/Pd
if P7 = BOM
Ac2O, py

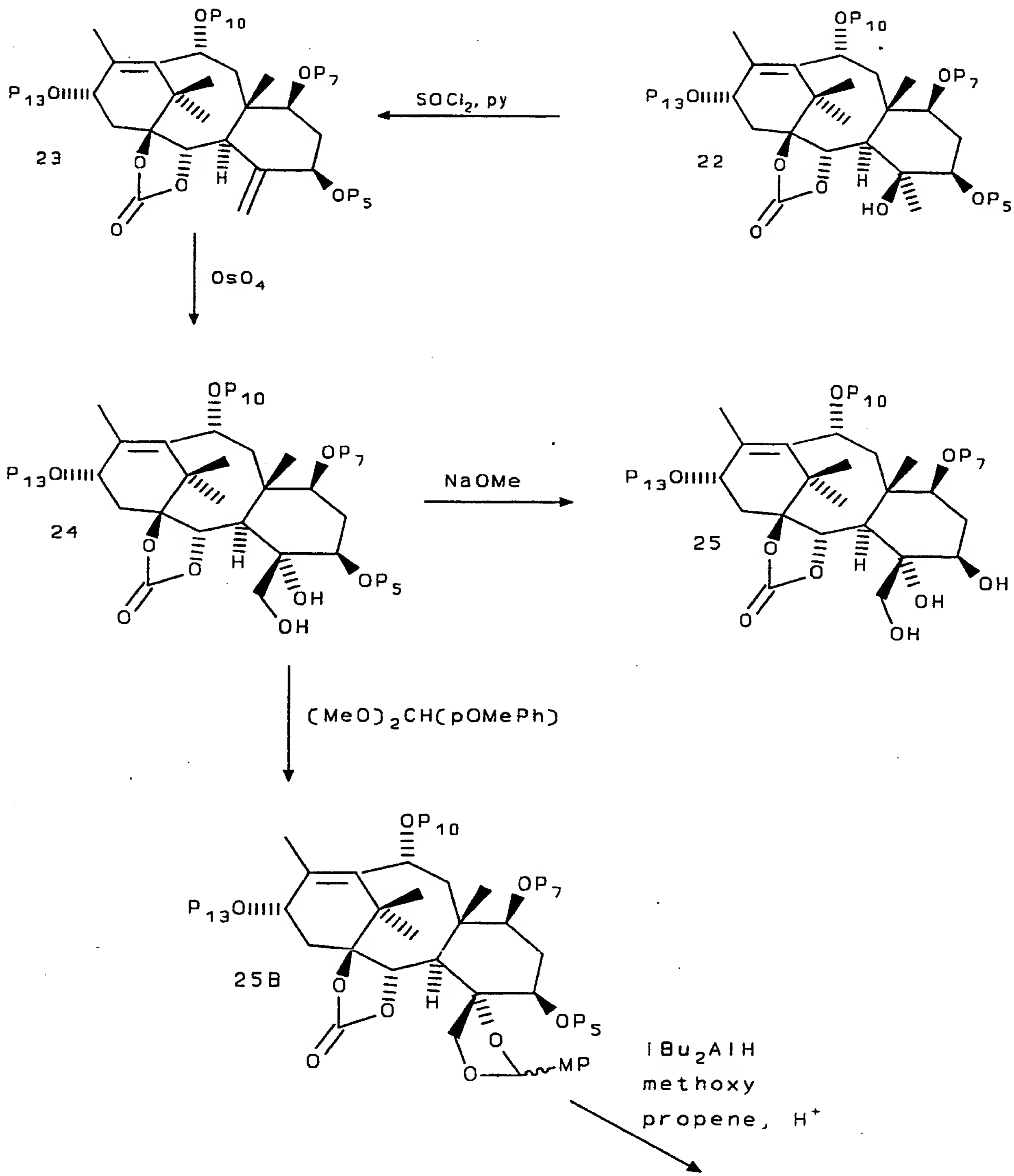


In Reaction Scheme A, P_5 is TMS, P_7 is MOP or BOM, P_{10} is TES, P_{13} is TBS, and R is ethyl in compounds 6 and 7, methyl in compounds 15, 16, and 17, Ms in compounds 24aa and 26a, and Ts in compound 26aa. It should be understood, however, that P_5, P_7, P_{10}, and P_{13} may be other hydroxy protecting groups and R may comprise other lower alkyl substituents in compounds 6, 7, 15, 16 and 17.

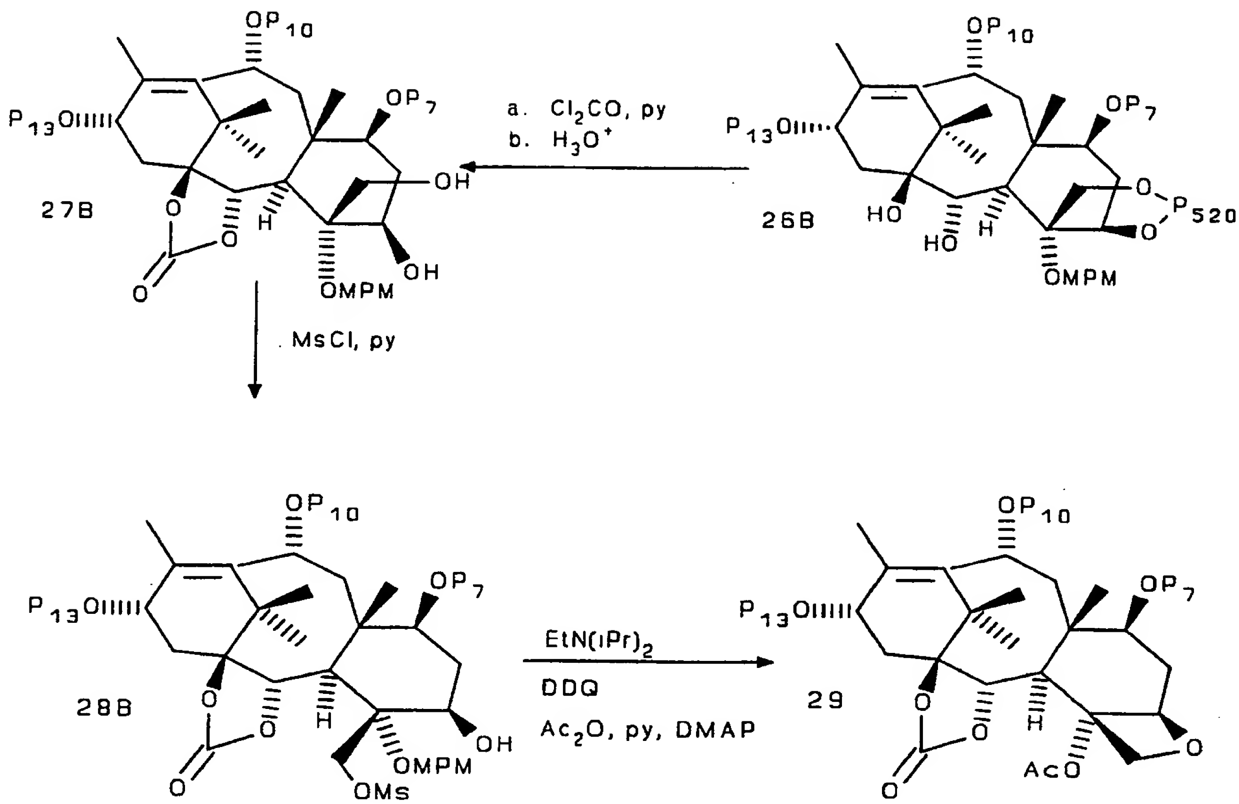
Reaction Scheme A may be varied between compounds 18 and 29 as set forth below in Reaction Scheme A', with the reactions leading to compound 18 and following compound 29 being as set forth in Reaction Scheme A.

Reaction Scheme A'



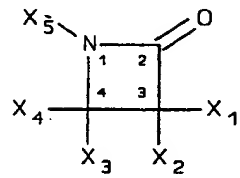


23 22 24 25 25B

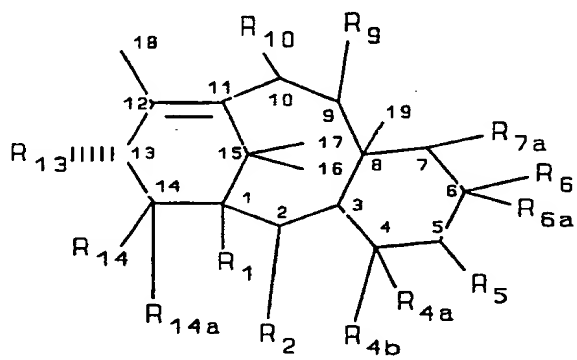


In Reaction Scheme A', P_5 is TMS or Ac, P_7 is MOP or BOM, P_{10} is TES, P_{13} is TBS and P_{520} is acetal or ketal, preferably acetonide. It should be understood, however, that P_5, P_7, P_{10}, and P_{13} and P_{520} may be other hydroxy protecting groups.

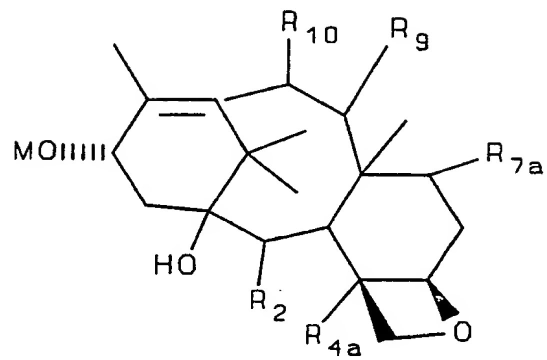
In general, tricyclic and tetracyclic taxanes bearing C13 side chains may be obtained by reacting a ß-lactam with alkoxides having the taxane tricyclic or tetracyclic nucleus and a C-13 metallic oxide substituent to form compounds having a ß-amido ester substituent at C-13. The ß-lactams have the following structural formula:



wherein X_1 - X_5 are as defined above. The alkoxides having the tricyclic or tetracyclic taxane nucleus and a C-13 metallic oxide or ammonium oxide substituent have the following structural formula:



wherein R_1, R_2, R_{4a}, R_{4b}, R_5, R_6, R_{6a}, R_{7a}, R_9, and R_{10} are as previously defined, R_{13} is -OM and M comprises ammonium or is a metal optionally selected from Group IA, IIA, transition (including lanthanides and actinides), IIB, IIIA IVA, VA, or VIA metals (CAS version). If M comprises ammonium, it is preferably tetraalkylammonium and the alkyl component of the tetraalkylammonium substituent is preferably C_1 - C_{10} alkyl such as methyl or butyl. Most preferably, the alkoxide has the tetracyclic taxane nucleus and corresponds to the structural formula:



wherein M, R_2, R_{4a}, R_{7a}, R_9, and R_{10} are as previously defined.

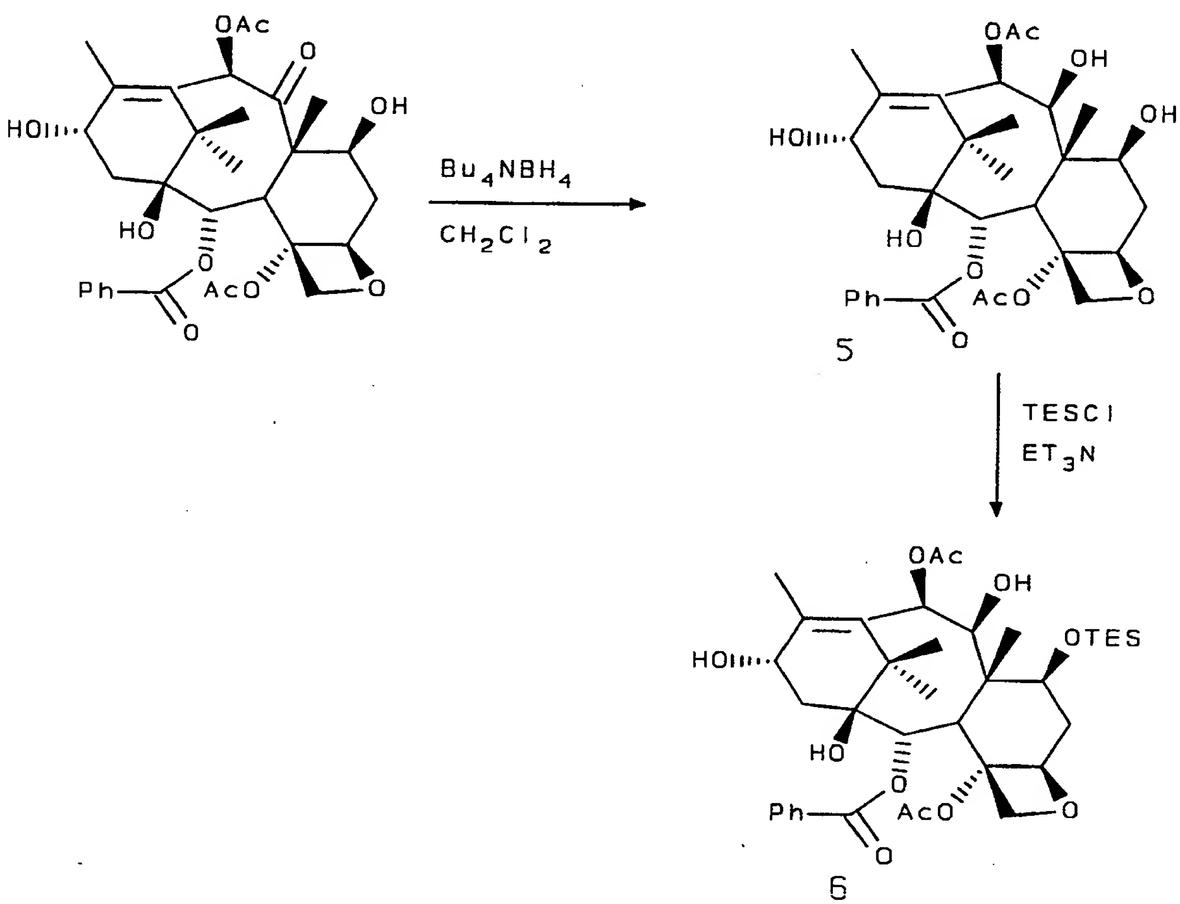
As set forth in Reaction Scheme A, taxol may be prepared by converting 7-protected Baccatin III **35** to the corresponding alkoxide and reacting the alkoxide with a β-lactam in which X_1 is protected hydroxy, X_3 is phenyl and X_5 is benzoyl. Protecting groups such as 2-methoxypropyl ("MOP"), 1-ethoxyethyl ("EE") are preferred, but a variety of other standard protecting groups such as the triethylsilyl group or other trialkyl (or aryl) silyl groups may be used. Taxanes having alternative side chain subsituents may be prepared through the use of β-lactams which comprise the alternative substituents.

Taxanes having alternative C9 substituents may be prepared by selectively reducing the C9 keto substituent of taxol, 10-DAB, Baccatin III or one of the other intermediates disclosed herein to yield the corresponding C9 β-hydroxy derivative. The reducing agent is preferably a borohydride and, most preferably, tetrabutylammoniumboro-hydride (Bu_4NBH_4) or triacetoxyborohydride.

As illustrated in Reaction Scheme 1, the reaction of baccatin III with Bu_4NBH_4 in methylene chloride yields 9-desoxo-9β-hydroxybaccatin III **5**. After the C7 hydroxy group is protected with the triethylsilyl protecting group, for example, a suitable side chain may

be attached to 7-protected-9ß-hydroxy derivative **6** as elsewhere described herein. Removal of the remaining protecting groups thus yields 9β-hydroxy-desoxo taxol or other 9β-hydroxytetracylic taxane having a C13 side chain.

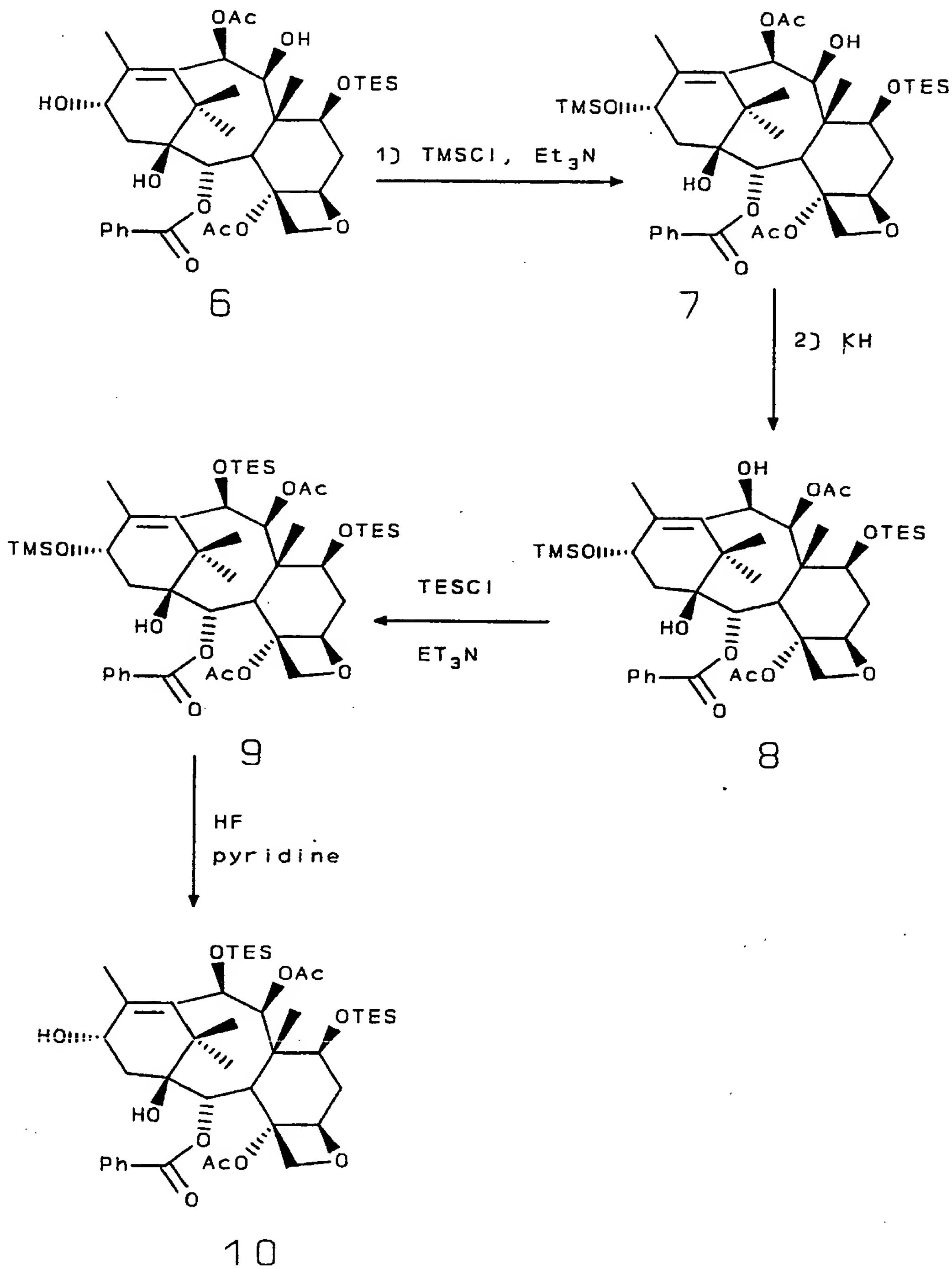
REACTION SCHEME 1



Alternatively, the C13 hydroxy group of 7-protected-9β-hydroxy derivative **6** may be protected with trimethylsilyl or other protecting group which can be selectively removed relative to the C7 hydroxy protecting group as illustrated in Reaction Scheme 2, to enable further selective manipulation of the various substituents of the taxane. For example, reaction of

7,13-protected-9β-hydroxy derivative **7** with KH causes the acetate group to migrate from C10 to C9 and the hydroxy group to migrate from C9 to C10, thereby yielding 10-desacetyl derivative **8**. Protection of the C10 hydroxy group of 10-desacetyl derivative **8** with triethylsilyl yields derivative **9**. Selective removal of the C13 hydroxy protecting group from derivative **9** yields derivative **10** to which a suitable side chain may be attached as described above.

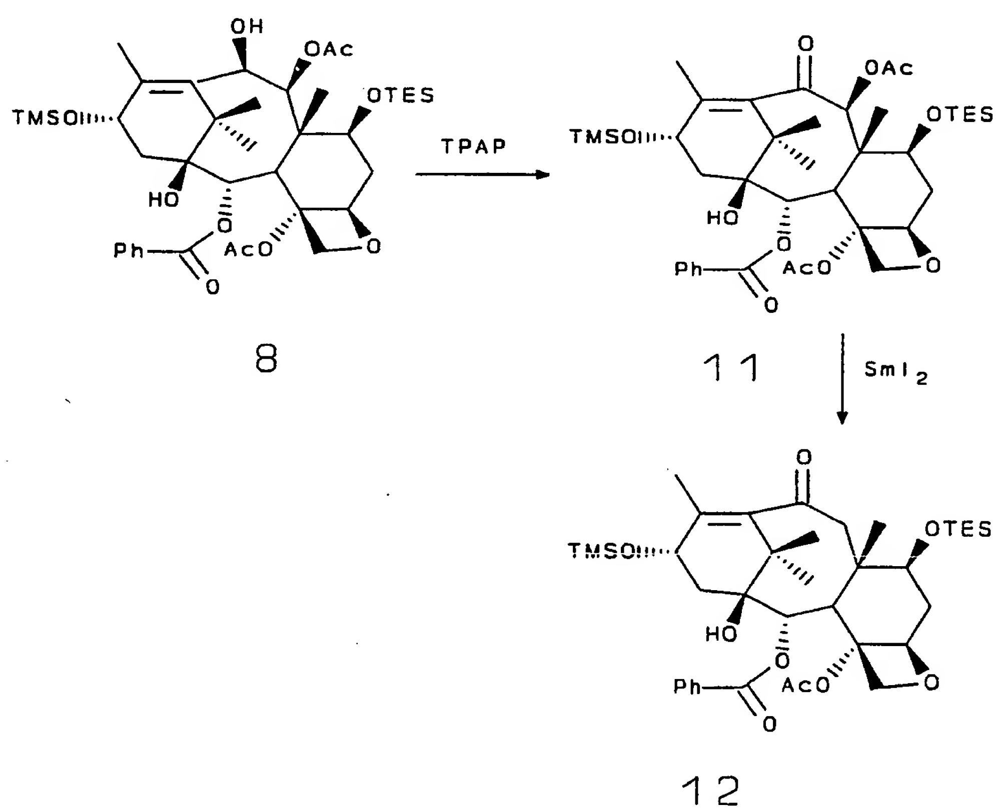
REACTION SCHEME 2



As shown in Reaction Scheme 3, 10-oxo derivative **11** can be provided by oxidation of 10-desacetyl derivative **8**. Thereafter, the C13 hydroxy

protecting group can be selectively removed followed by attachment of a side chain as described above to yield 9-acetoxy-10-oxo-taxol or other 9-acetoxy-10-oxotetracylic taxanes having a C13 side chain. Alternatively, the C9 acetate group can be selectively removed by reduction of 10-oxo derivative **11** with a reducing agent such as samarium diiodide to yield 9-desoxo-10-oxo derivative **12** from which the C13 hydroxy protecting group can be selectively removed followed by attachment of a side chain as described above to yield 9-desoxo-10-oxo-taxol or other 9-desoxo-10-oxotetracylic taxanes having a C13 side chain.

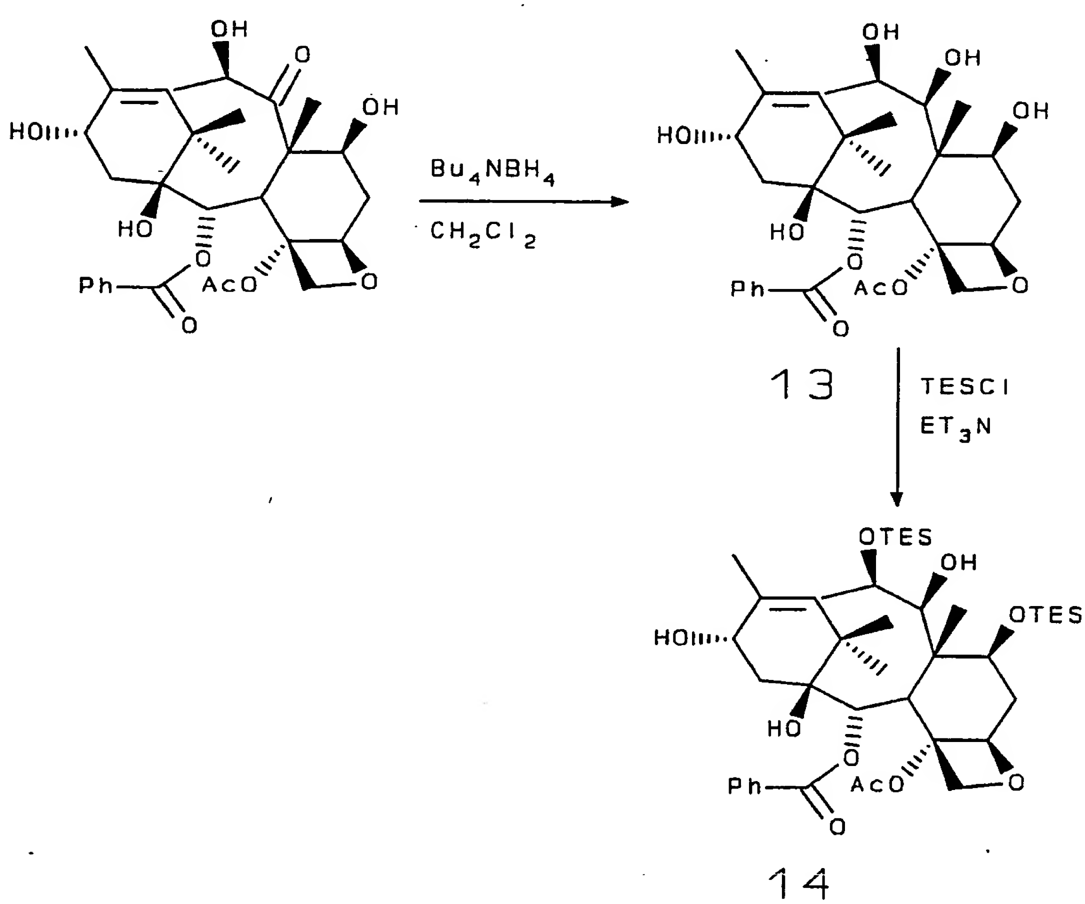
REACTION SCHEME 3



Reaction Scheme 4 illustrates a reaction in which 10-DAB is reduced to yield pentaol **13**. The C7 and

C10 hydroxyl groups of pentaol **13** can then be selectively protected with the triethylsilyl or another protecting group to produce triol **14** to which a C13 side chain can be attached as described above or, alternatively, after further modification of the tetracylic substituents.

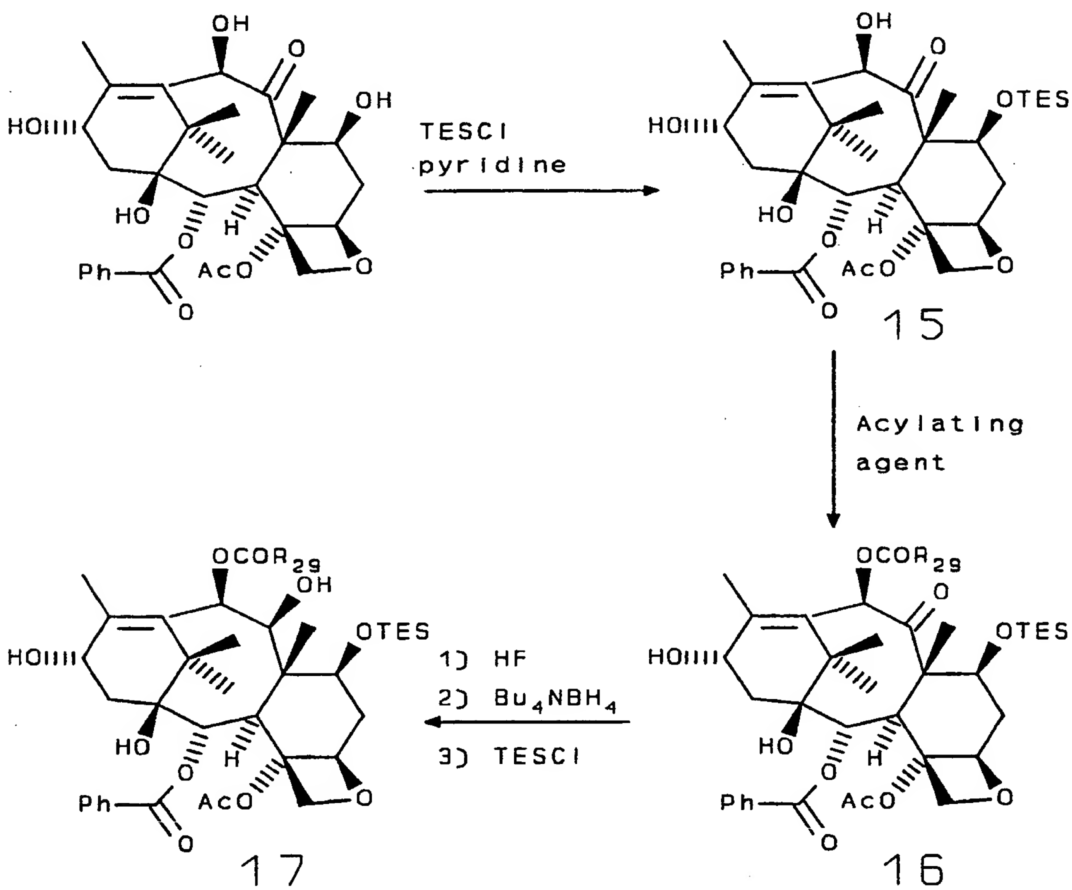
REACTION SCHEME 4



Taxanes having C9 and/or C10 acyloxy substituents other than acetate can be prepared using 10-DAB as a starting material as illustrated in Reaction Scheme 5. Reaction of 10-DAB with triethylsilyl chloride in pyridine yields 7-protected 10-DAB **15**. The C10 hydroxy substituent of 7-protected 10-DAB **15** may then be readily acylated with any standard acylating agent to

yield derivative **16** having a new C10 acyloxy substituent. Selective reduction of the C9 keto substituent of derivative **16** yields 9ß-hydroxy derivative **17** to which a C13 side chain may be attached. Alternatively, the C10 and C9 groups can be caused to migrate as set forth in Reaction Scheme **2**, above.

REACTION SCHEME 5



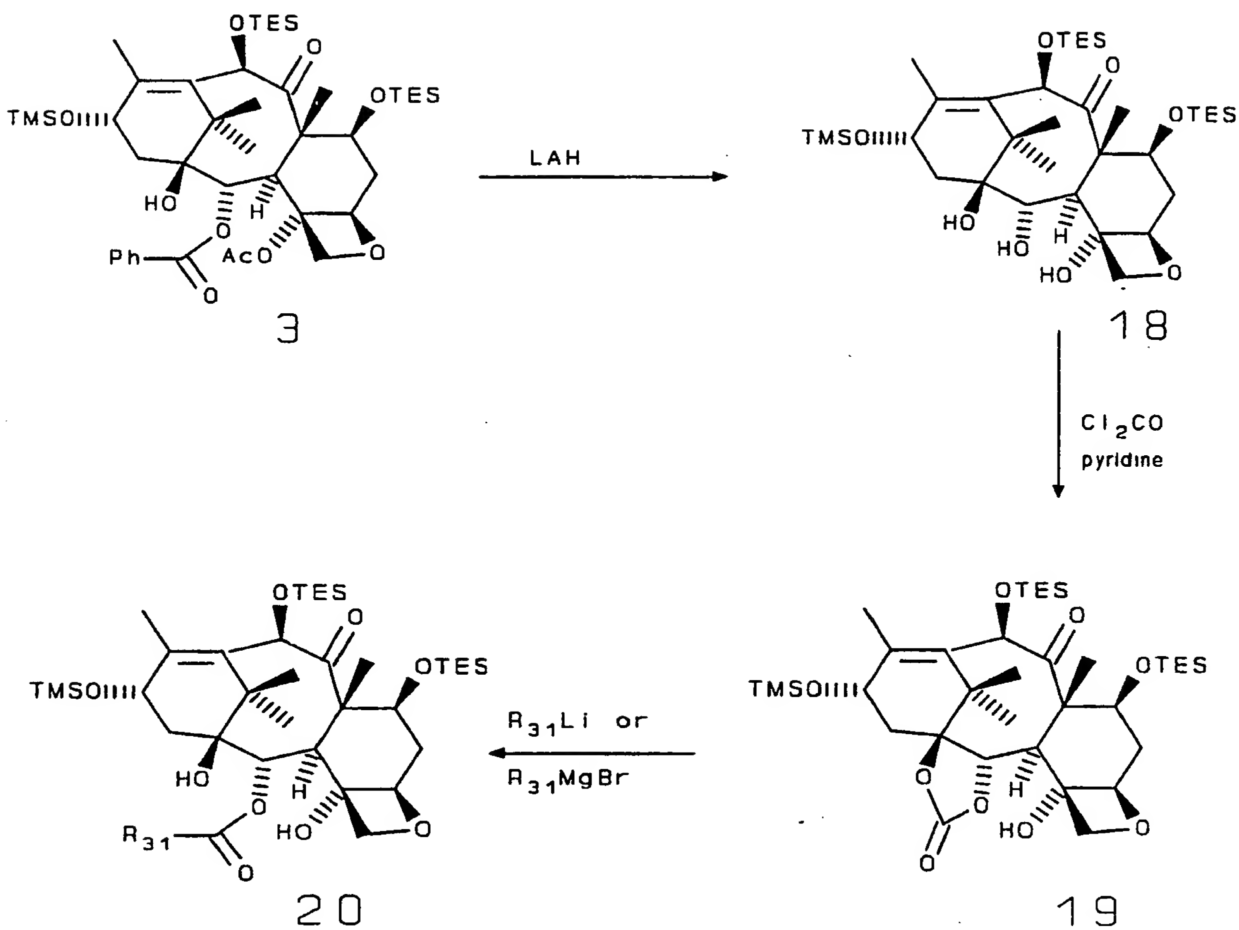
Taxanes having alternative C2 and/or C4 esters can be prepared using baccatin III and 10-DAB as starting materials. The C2 and/or C4 esters of baccatin III and 10-DAB can be selectively reduced to the corresponding alcohol(s) using reducing agents such as LAH or Red-Al, and new esters can thereafter be substituted using

standard acylating agents such as anhydrides and acid chlorides in combination with an amine such as pyridine, triethylamine, DMAP, or diisopropyl ethyl amine. Alternatively, the C2 and/or C4 alcohols may be converted to new C2 and/or C4 esters through formation of the corresponding alkoxide by treatment of the alcohol with a suitable base such as LDA followed by an acylating agent such as an acid chloride.

Baccatin III and 10-DAB analogs having different substituents at C2 and/or C4 can be prepared as set forth in Reaction Schemes 6-10. To simplify the description, 10-DAB is used as the starting material. It should be understood, however, that baccatin III derivatives or analogs may be produced using the same series of reactions (except for the protection of the C10 hydroxy group) by simply replacing 10-DAB with baccatin III as the starting material. 9-desoxo derivatives of the baccatin III and 10-DAB analogs having different substituents at C2 and/or C4 can then be prepared by reducing the C9 keto substituent of these analogs and carrying out the other reactions described above.

In Reaction Scheme 6, protected 10-DAB **3** is converted to the triol **18** with lithium aluminum hydride. Triol **18** is then converted to the corresponding C4 ester using Cl_2CO in pyridine followed by a nucleophilic agent (e.g., Grignard reagents or alkyllithium reagents).

Scheme 6

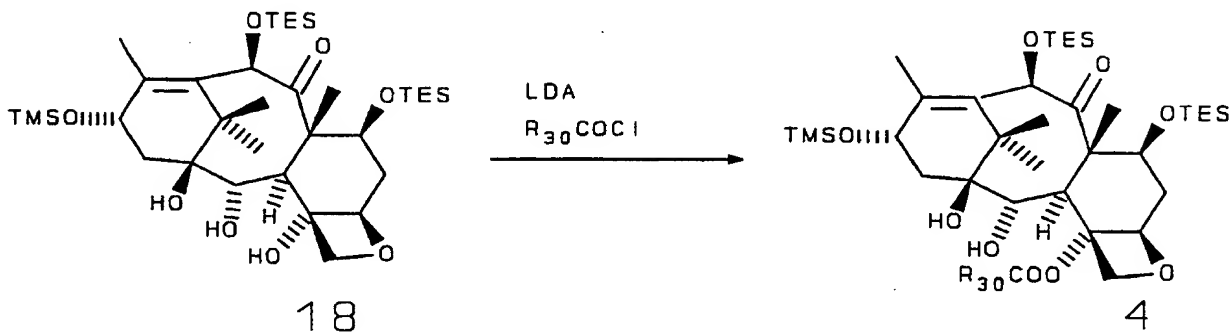


Deprotonation of triol **18** with LDA followed by introduction of an acid chloride selectively gives the C4 ester. For example, when acetyl chloride was used, triol **18** was converted to 1,2 diol **4** as set forth in Reaction Scheme 7.

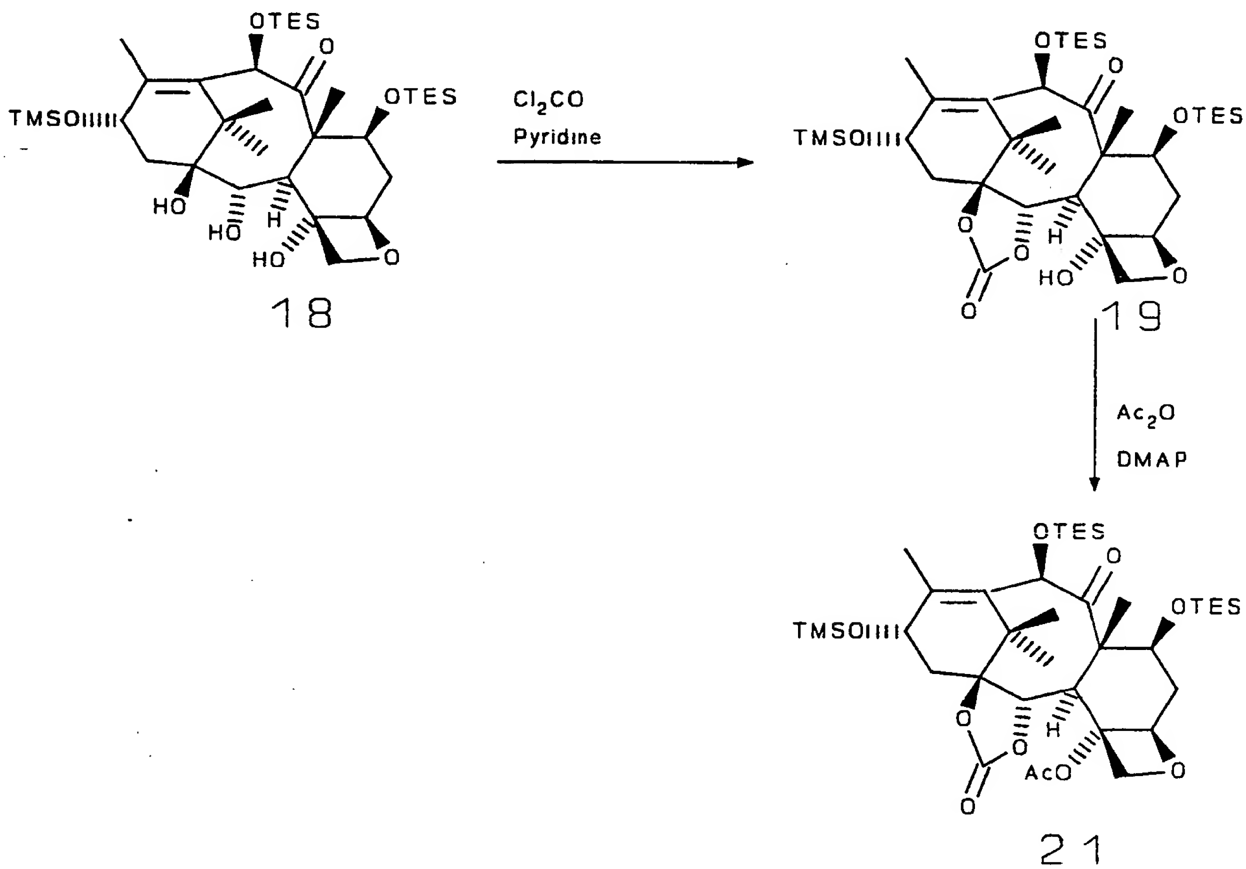
Triol **18** can also readily be converted to the 1,2 carbonate **19**. Acetylation of carbonate **19** under vigorous standard conditions provides carbonate **21** as described in Reaction Scheme 8; addition of alkyllithiums or Grignard reagents to carbonate **19** provides the C2

ester having a free hydroxyl group at C4 as set forth in Reaction Scheme 6.

Scheme 7

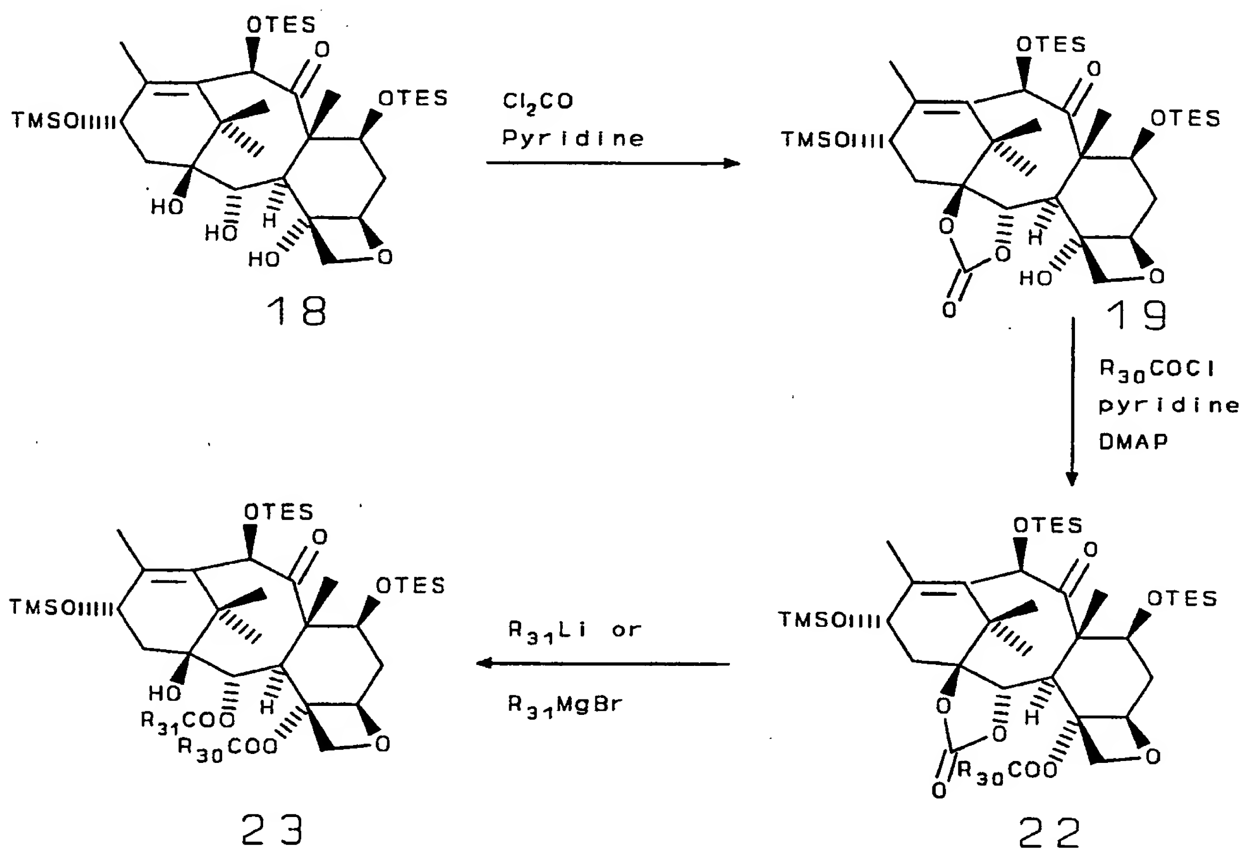


Scheme 8



As set forth in Reaction Scheme 9, other C4 substituents can be provided by reacting carbonate **19** with an acid chloride and a tertiary amine to yield carbonate **22** which is then reacted with alkyllithiums or Grignard reagents to provide 10-DAB derivatives having new substituents at C2.

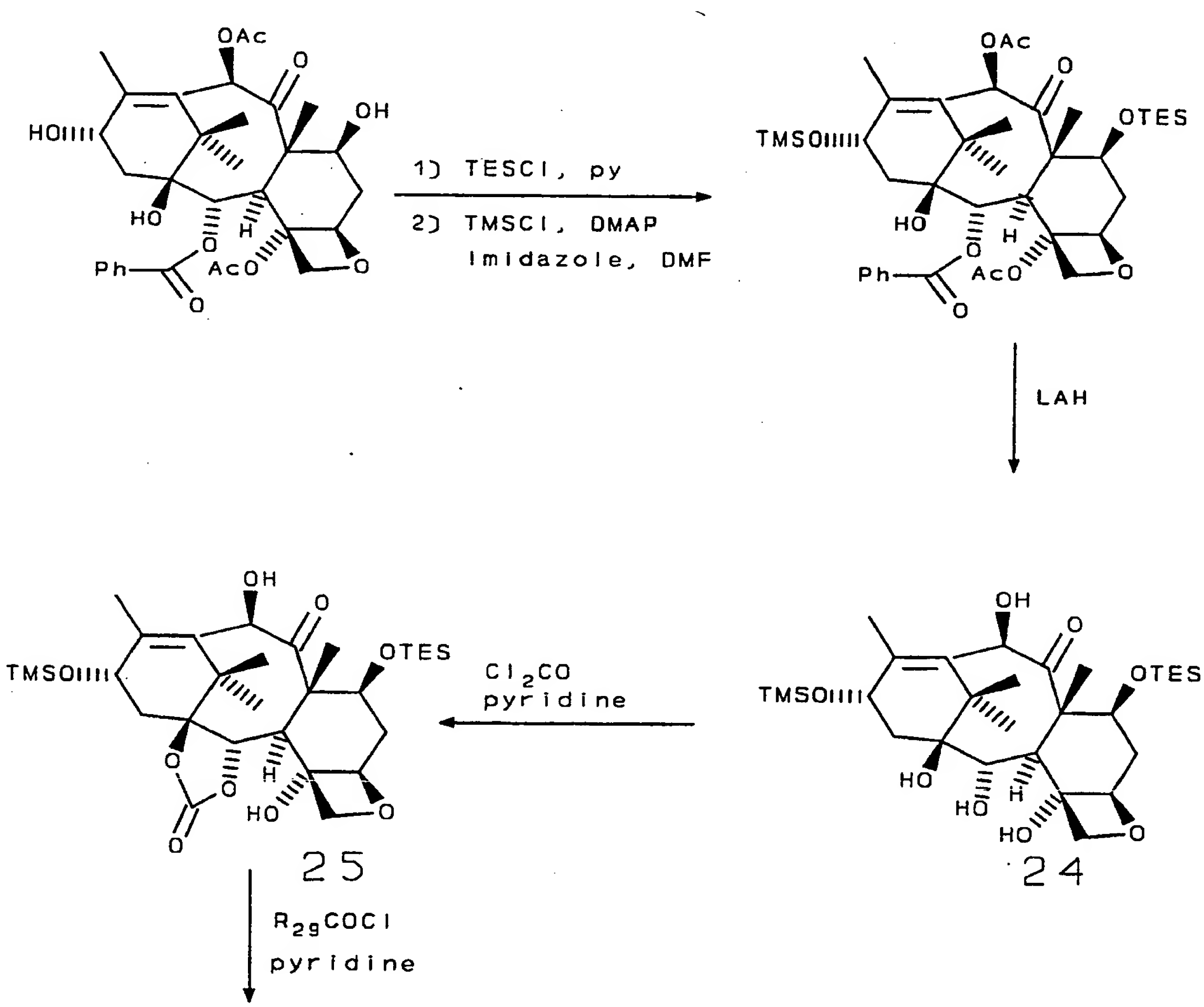
Scheme 9



Alternatively, baccatin III may be used as a starting material and reacted as shown in Reaction Scheme 10. After being protected at C7 and C13, baccatin III is reduced with LAH to produce 1,2,4,10 tetraol **24**. Tetraol **24** is converted to carbonate **25** using Cl_2CO and pyridine, and carbonate **25** is acylated at C10 with an acid chloride

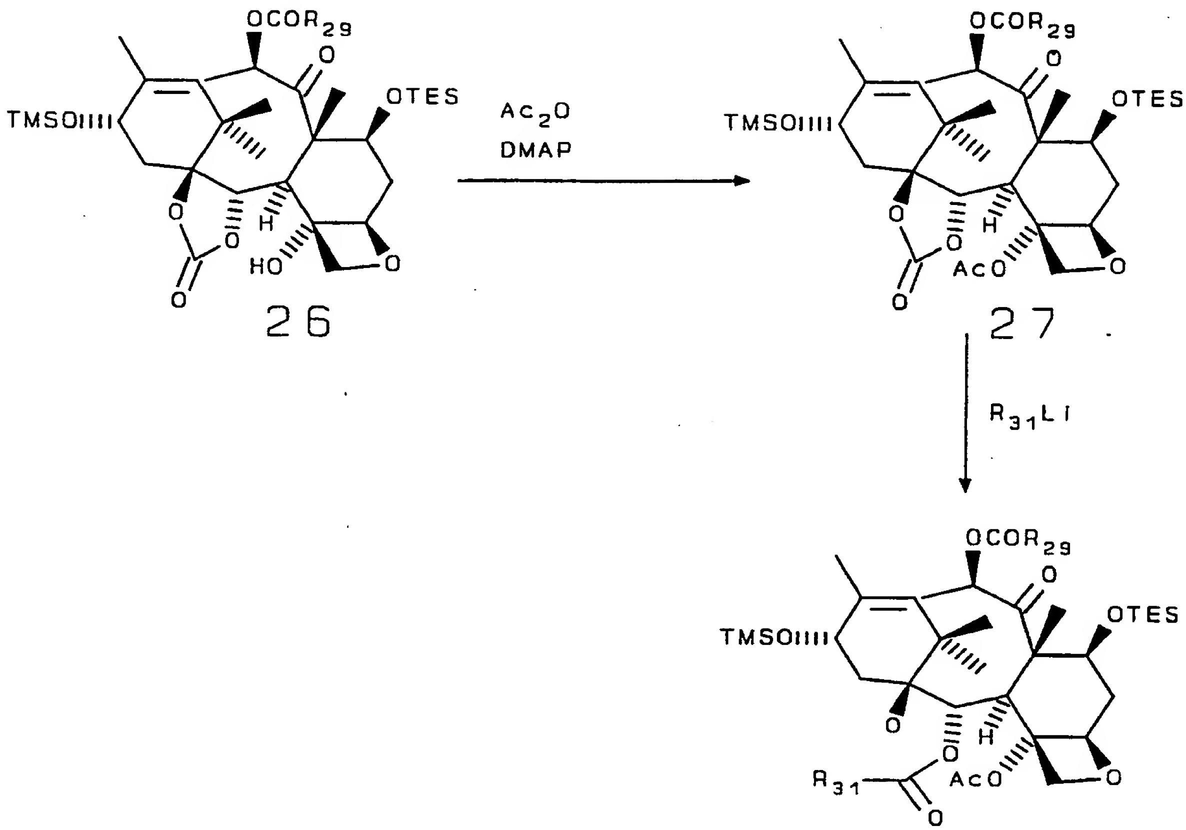
and pyridine to produce carbonate **26** (as shown) or with acetic anhydride and pyridine (not shown). Acetylation of carbonate **26** under vigorous standard conditions provides carbonate **27** which is then reacted with alkyl lithiums to provide the baccatin III derivatives having new substituents at C2 and C10.

Scheme 10



25

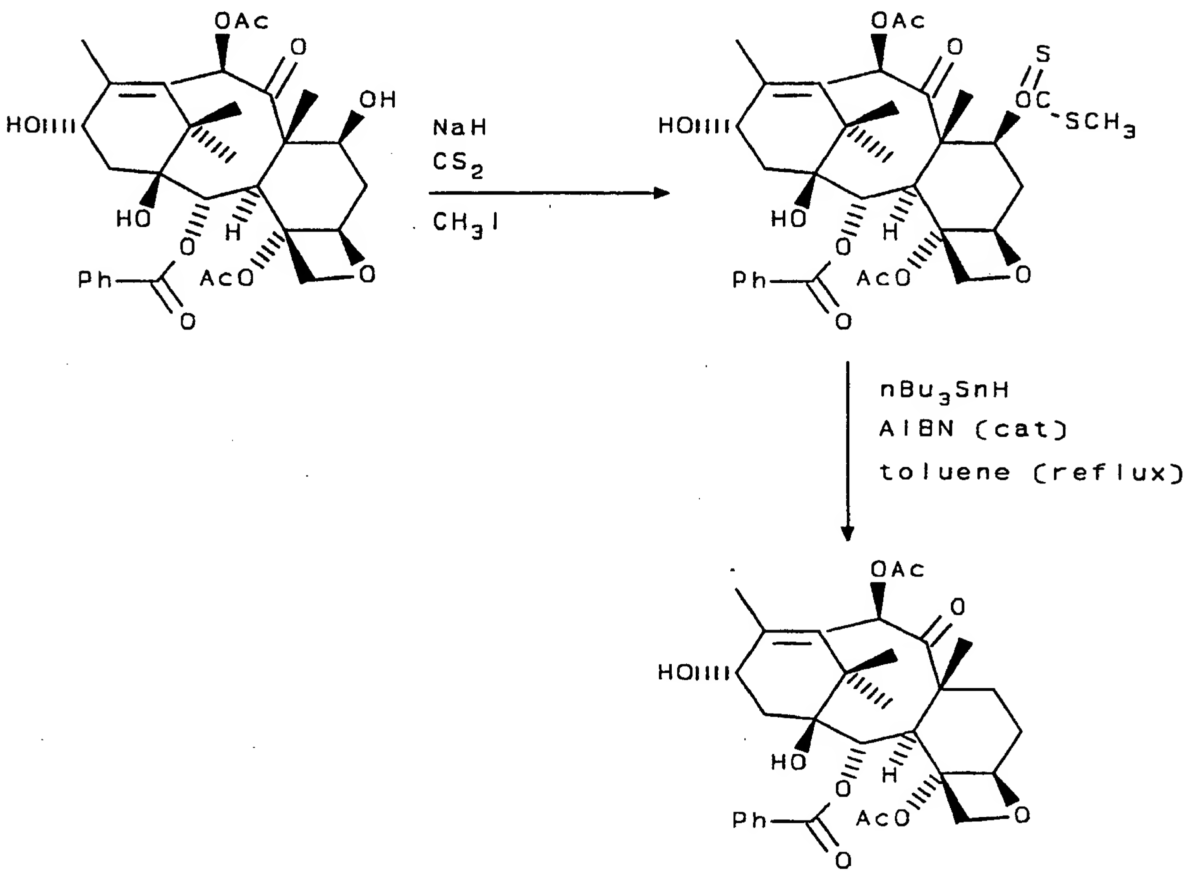
24



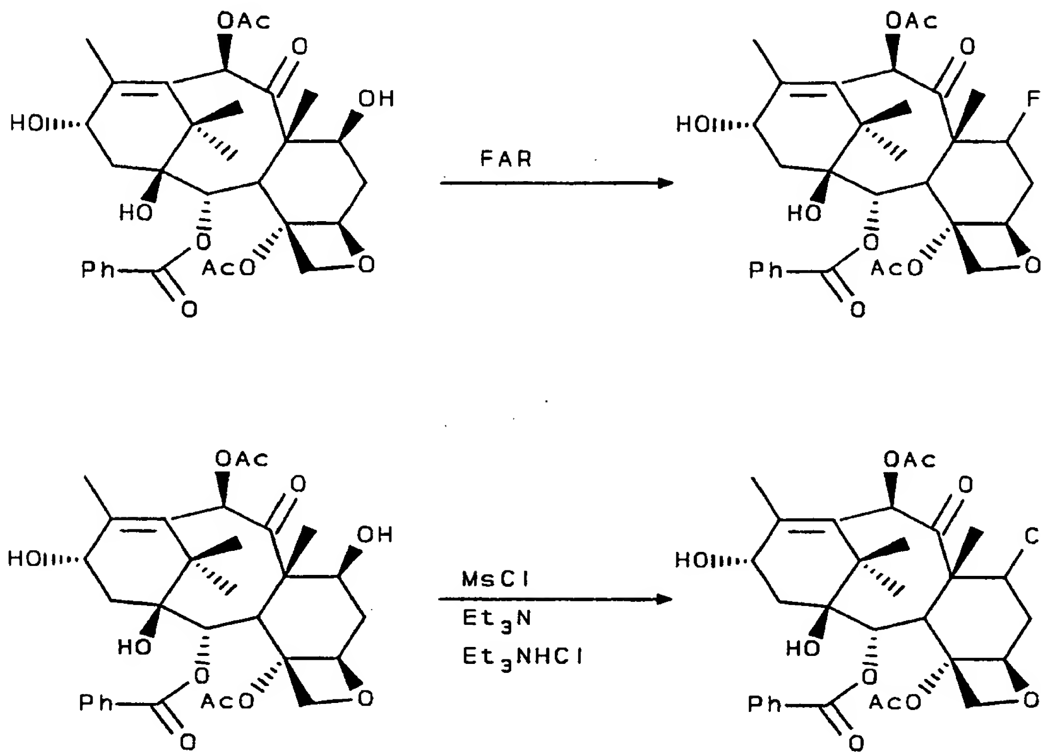
10-desacetoxy derivatives of baccatin III and 10-desoxy derivatives of 10-DAB may be prepared by reacting baccatin III or 10-DAB (or their derivatives) with samarium diiodide. Reaction between the tetracyclic taxane having a C10 leaving group and samarium diiodide may be carried out at 0°C in a solvent such as tetrahydrofuran. Advantageously, the samarium diiodide selectively abstracts the C10 leaving group; C13 side chains and other substituents on the tetracyclic nucleus remain undisturbed. Thereafter, the C9 keto substituent may be reduced to provide the corresponding 9-desoxo-9β-hydroxy-10-desacetyoxy or 10-desoxy derivatives as otherwise described herein.

C7 dihydro and other C7 substituted taxanes can be prepared as set forth in Reaction Schemes 11, 12 and 12a.

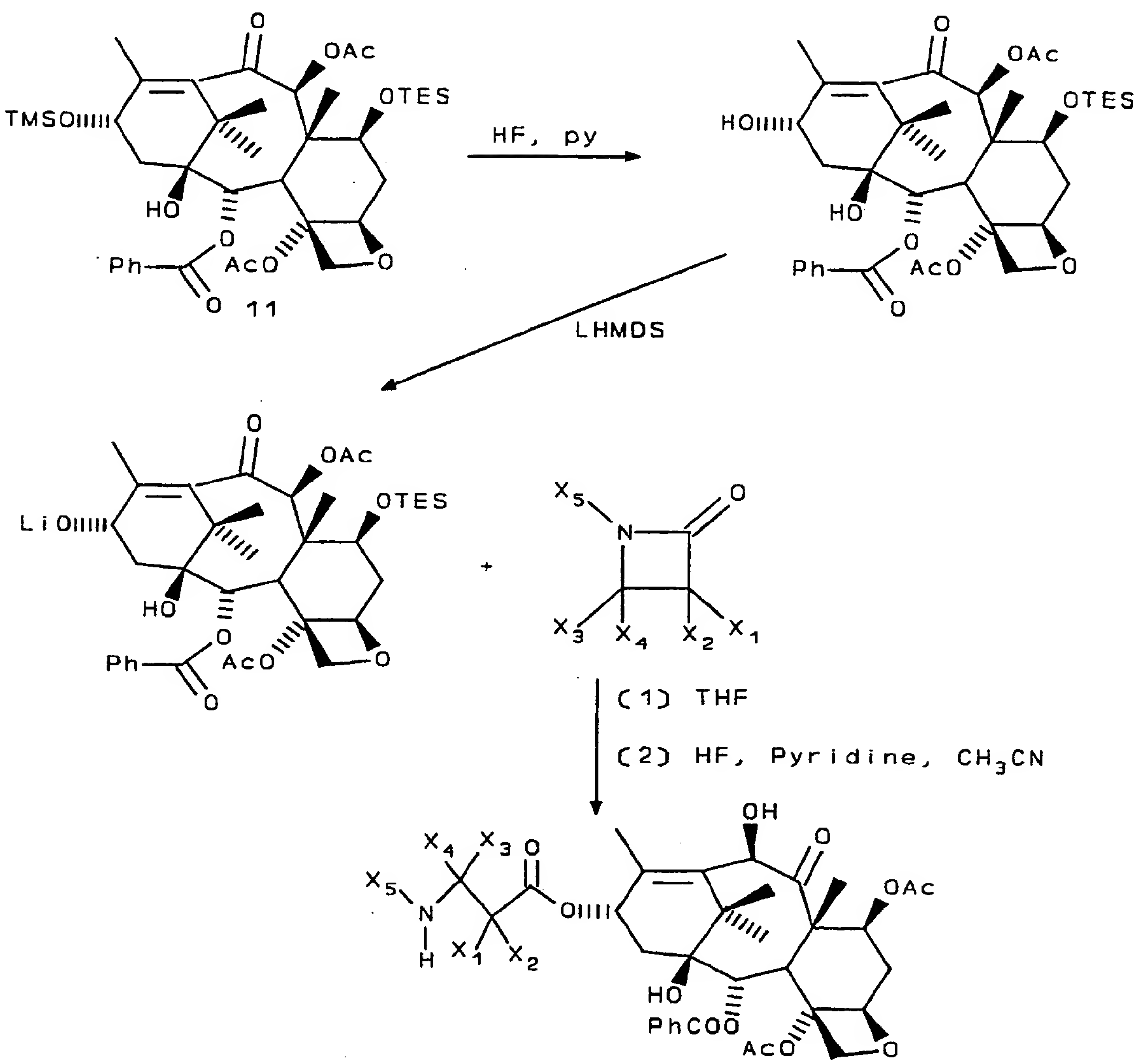
REACTION SCHEME 11



REACTION SCHEME 12



REACTION SCHEME 12a

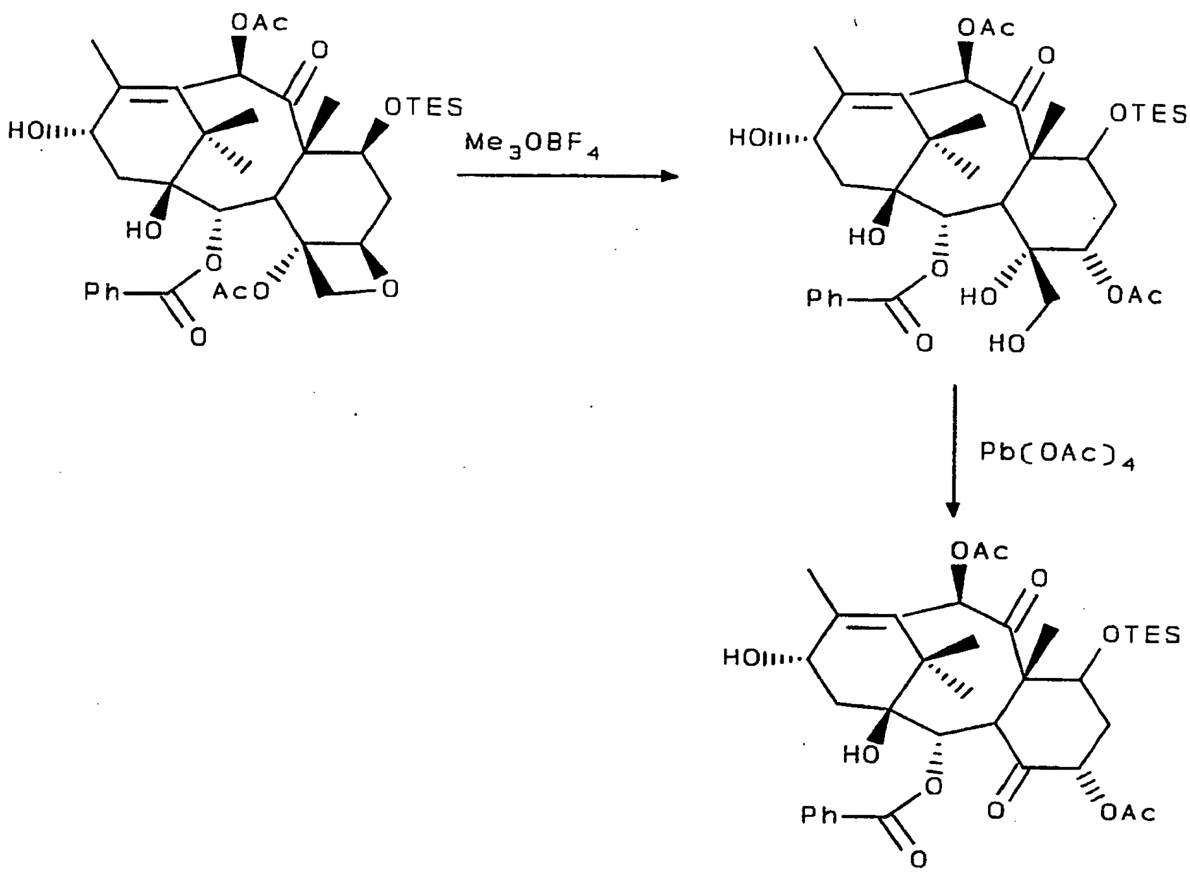


As shown in Reaction Scheme 12, Baccatin III may be converted into 7-fluoro baccatin III by treatment with FAR at room temperature in THF solution. Other baccatin derivatives with a free C7 hydroxyl group behave similarly. Alternatively, 7-chloro baccatin III can be prepared by treatment of baccatin III with methane sulfonyl chloride and triethylamine in methylene chloride solution containing an excess of triethylamine hydrochloride.

Taxanes having C7 acyloxy substituents can be prepared as set forth in Reaction Scheme 12a, 7,13-protected 10-oxo-derivative 11 is converted to its corresponding C13 alkoxide by selectively removing the C13 protecting group and replacing it with a metal such as lithium. The alkoxide is then reacted with a β-lactam or other side chain precursor. Subsequent hydrolysis of the C7 protecting groups causes a migration of the C7 hydroxy substituent to C10, migration of the C10 oxo substituent to C9, and migration of the C9 acyloxy substituent to C7.

As shown in Reaction Scheme 13, 7-O-triethylsilyl baccatin III can be converted to a tricyclic taxane through the action of trimethyloxonium tetrafluoroborate in methylene chloride solution. The product diol then reacts with lead tetraacetate to provide the corresponding C4 ketone.

REACTION SCHEME 13



The subprocesses of Reaction scheme A can be applied at various stages. For example, the process for the conversion of compound 30 to compound 33 can be applied to any intermediate having a hydroxyl group at C-10 and two hydrogens at C-9, e.g., the process for introducing C9 and C10 carbonyl and hydroxyl groups can be applied to suitably protected intermediates 4 through 29.

Likewise, the process for introduction of C1 and C2 oxygen-containing functional groups (conversion of 6 to 13 in Reaction Scheme A) can be applied to any intermediate having a C3 carbonyl group.

Similarly, the process for introducing C2 and C4 acyl groups as exemplified in Reaction Schemes 6 through 10 can be applied to any intermediate having a C1, C2 carbonate.

Also, the process for forming the oxetane ring, as exemplified in the conversion of 24a to 27a in Reaction Scheme A, can be applied to a variety of intermediates having a C4 carbonyl group.

The aldol process exemplified in the conversion of 5 to 6 in Reaction Scheme A can be applied to any suitably protected intermediate having a C3 carbonyl group and a C8a hydrogen. A variety of ketones or aldehydes can be used as a reactant in this process.

Formation of a cyclic carbonate from any 1,2 or 1,3 diol subunit in any intermediate can be carried out by using phosgene as a reactant. Carbonyl groups can be reduced by hydride reagents or metallic species to the corresponding alcohols. Alcohols can be oxidized using a variety of oxidizing agents as exemplified in the Reaction Schemes, to the corresponding carbonyl groups.

The compounds disclosed in this application have several asymmetric carbons and may exist in diastereomeric, racemic, or optically active forms. All of these forms are contemplated within the scope of this invention. More specifically, the present invention includes the enantiomers, diasteriomers, racemic mixtures, and other mixtures of the compounds disclosed herein.

The following examples illustrate the invention.

EXAMPLES

REACTION SCHEME A

Triethylsilyloxy alcohol 3. To a solution of diol 2 (3.16 g, 13.4 mmol) and DMAP (70 mg, 0.57 mmol) in CH_2Cl_2 (65 mL) at room temperature was added triethylamine (3.7 mL, 26.6 mmol) followed by dropwise addition of TESCl (2.7 mL, 16.1 mmol). After 1.75 h, the reaction mixture was diluted with 150 mL of hexane, then poured into 100 mL of a saturated aqueous $NaHCO_3$ solution and 150 mL of hexane. The organic phase was washed with two 100 mL portions of saturated aqueous $NaHCO_3$ solution and with 100 mL of water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 4.88 g of crude triethylsilyloxyalcohol 3. An analytical sample was obtained by plug filtration through a short pad of silica gel washing with hexane and then eluting the pure compound 3 (P_{10} = TES) (colorless oil) with 5% ethyl acetate in hexane.

3 (P_{10} = TES): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.61 (q, J = 7.7 Hz, 6H, TES CH_2), 0.89 (s, 3H, CH_3 16), 0.96 (t, J = 7.7 Hz, 9H, TES CH_3), 1.03 (d, J = 7.1 Hz, 3H, CH_3 19), 1.07 (s, 3H, CH_3 17), 1.23 (d, J = 14.3 Hz, 1H, H2α), 1.56 (dd, J = 6.0, 6.0 Hz, 1H, H7), 1.76 (ddd, J = 5.0, 11.0, 13.7 Hz, 1H, H9), 1.90 (ddd, J = 2.2, 8.8, 15.4 Hz, 1H, H9), 1.96 (m, 1H, H14α), 2.37 (m, 2H, H2β, H14β), 2.51 (ddd, J = 7.7, 7.7, 10.4 Hz, 1H, H8α), 2.94 (s, 1H, OH-3), 4.21 (dd, J = 2.2, 5.0 Hz, 1H, H10), 5.43 (dd, J = 2.8, 2.8 Hz, 1H, H13). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 4.8 (TES CH_2), 6.7 (TES CH_3), 15.02 (CH_3 19), 23.0 (CH_3 17), 26.2 (CH_3 18), 28.0 (CH_3 16), 33.6 (C14), 41.5 (C8), 44.2 (C2), 45.0 (C1), 45.2 (C15), 45.8 (C9), 69.6 (C11), 74.9 (C10), 96.0 (C3), 123.0 (C13), 143.7 (C12); IR ($CHCl_3$) υ 3530, 2970, 2930, 2900, 1460, 1340, 1140, 1100, 1080, 1045, 1010, 970, 915, 650 cm^{-1}; MS (CI) 351 (M+1, 58), 333 (100), 219 (34).

Hydroxy Ketone 4. To a vigorously stirred solution of the crude compound 3 (P_{10} = TES) in anhydrous CH_2Cl_2 (30 mL) at 0 °C under nitrogen was added Ti $(O^iPr)_4$ (13.5 mL, 43.1 mmol) followed by dropwise addition of anhydrous 2M ^{t}-BuOOH in hexane (18 mL, 36 mmol). After 45 min dimethylsulfide (15 mL) was added slowly over a period of 5 min. The solution was stirred for 10 min at 0 °C, then 15 min at room temperature and then moved to a 55 °C bath where it was

heated under reflux for 8h. The solvents were evaporated under reduced pressure, the resulting thick syrup was dissolved in ethyl acetate (850 mL) and 3.5 mL of H_2O was added dropwise with vigorous stirring. The resulting mixture was stirred at room temperature for 1h and then filtered through a pad of Celite which was further washed with two protions of 100 mL of ethyl acetate. Evaporation of the solvent under reduced pressure afforded an oil that was filtered through a short pad of silica gel eluting with 10% ethyl acetate in hexane to give 4.78 g of pure hydroxyketone 4 (P_{10} = TES) (colorless oil).

4 (P_{10} = TES): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.58 (q, J = 7.7 Hz, 6H, TES CH_2), 0.94 (t, J = 7.7 Hz, 12H, CH_3 19, TES CH_3), 0.98 (s, 3H, CH_3 17), 1.31 (s, 3H, CH_3 16), 1.71 (dd, J = 5.0, 11.5 Hz, 1H, H2α), 1.85 (m, 3H, H1, H9β, H14β), 1.96 (s, 3H, CH_3 18), 2.15 (d, J = 12.1, 1H, OH-13), 2.22 (ddd, J = 4.9, 13.2, 15.9 Hz, 1H, H9α), 2.56 (dddd, J = 3.8, 7.1, 13.7, 13.7 Hz, 1H, H8α), 2.75 (dd, J = 2.2, 11.0 Hz, 1H, H2β), 2.80 (ddd, J = 4.4, 7.7, 11.0 Hz, 1H, H14β), 4.10 (t, J = 11.0 HZ, 1H, H13β), 4.56 (d, J = 5.0 Hz, 1H, H10β); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 4.3 (TES CH_2), 6.5 (TES CH_3), 13.4 (CH_3 18), 18.4 ($CH_3$19), 25.8 (CH_3 17), 27.1 (CH_3 16), 34.7 (C14), 38.2 (C15), 38.8 (C2), 44.0 (C8), 44.2 (C9), 47.8 (C1), 67.3 (C13), 69.7 (C10), 137.3 (C11), 138.8 (C12), 219.2 (C3); IR ($CHCl_3$) υ 3550, 2960, 2880, 1660, 1460, 1410, 1240, 1200, 1160, 1140, 1080, 1050, 1000, 980, 900, 810 cm^{-1}; MS (CI) 367 (M+1, 2), 349 (100), 331 (55).

Ketone 5. To a solution of hydroxyketone 4 (P_{10} = TES) in anhydrous pyridine (25 mL) at -23 °C under nitrogen was added dropwise TBSOTf (3.2 mL, 13.9 mmol). After 5 min, the flask was moved to an ice bath and stirred for 1.75 h. The solution was diluted with 75 mL of hexane at 0 °C and then decanted from the insoluble oil into saturated aqueous $NaHCO_3$ solution (200 mL). The remaining oil was extracted with three 75 mL portions of hexane. The combined organic phases were washed with two 50 mL portions of saturated aqueous $NaHCO_3$ solution and then with 50 mL of water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The yellowish oily residue was purified by filtration through a short pad of silica gel eluting with 10% ethyl acetate in hexane to give 4.78 g of pure ketone 5 (P_{10} = TES, P_{13} = TBS) (94% yield from 2).

5 (P_{10} = TES, P_{13} = TBS): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H, TBS CH_3), 0.05 (s, 3H, TBS CH_3), 0.57 (q, J = 8.2 Hz, 6H, TES CH_2), 0.93 (t, J = 8.2 Hz, 9H, TES CH_3), 0.93 (s, 9H, TBS t-Bu), 0.96 (d, J = 1.8 Hz, 3H, CH_3 19), 1.06 (s, 3H, CH_3 17), 1.33 (s, 3H, CH_3 16), 1.68 (dd, J = 5.5, 11.5 Hz, 1H, H2α), 1.84 (m, 2H, H1, H9β), 1.89 (s, 3H, CH_3 18), 1.92 (dd, J = 6.0, 14.3 Hz, 1H, H14α), 2.21 (ddd, J = 5.5, 13.2, 15.4 Hz, 1H, H9α), 2.39 (ddd, J = 8.2, 10.4, 14.3 Hz, 1H, H14β), 2.52 (ddd, J = 3.9, 7.1, 13.6 Hz, 1H, H8α), 2.66 (dd, J = 2.8, 11.5 Hz, 1H, H2β), 4.45 (dd, J = 5.5, 10.4 Hz, 1H, H13β), 4.61 (d, J = 5.0 Hz, 1H, H10β); ^{13}C NMR δ (ppm) -5.4 (TBS CH_3), -4.6 (TBS CH_3), 4.3 (TES CH_2), 6.5 (TES CH_3), 14.1 (CH_3 18), 17.9 (TBS $\underline{C}(CH_3)_3$), 19.1 (CH_3 19), 25.4 (CH_3 17), 25.8 (TBS $C(\underline{C}H_3)_3$), 26.8 (CH_3 16), 33.5 (C14), 38.6 (C15), 39.4 (C2), 43.7 (C8), 44.4 (C9), 47.5 (C1), 67.5 (C13), 69.5 (C10), 136.8 (C11), 138.8 (C12), 213.5 (C3); IR ($CHCl_3$) υ 2950, 2900, 1680, 1460, 1420, 1395, 1365, 1250, 1200, 1110, 1080, 1000, 900, 860, 840 cm^{-1}; MS (CI) 481 (M+1, 3), 463 (16), 349 (100), 331 (50); Anal. Calcd. for $C_{27}H_{52}O_3Si_2$: C, 67.44; H, 10.90. Found: C, 67.31; H, 10.78.

Ketocarbonate 6. To a stirred solution of diisopropylamine (0.60 mL, 4.28 mmol) in THF (11 mL) under nitrogen at room temperature was added 1.26 mL of a 3.1 M solution (3.89 mmol) of MeMgBr in ether. After 3 h, a solution of ketone 5 (P_{10} = TES, P_{13} = TBS) (750 mg, 1.56 mmol) in THF (3.5 mL) was added dropwise at room temperature. After 1.5 h, the reaction mixture was cooled to -23 °C and a solution of 4-pentenal (327 mg, 3.89 mmol) in THF (4 mL) was added dropwise down the side of the flask. After 1 h, 10 mL of a saturated aqueous NH_4Cl solution was added. Ater 2 min, the reaction mixture was diluted with 100 mL of hexane, then poured into 100 mL of H_2O. The organic phase was washed with 100 mL of H_2O and 100 mL of brine, and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 0.92 g of a yellow oil. To a solution of the crude mixture in CH_2Cl_2 (10 mL) and pyridine (10 mL) under nitrogen at -23 °C was added 2.3 mL of 4 M solution (9.36 mmol) of phosgene in toluene dropwise and the reaction mixture was warmed to -10 °C. After 30 min, ethanol (3.7 mL) was added and the resulting mixture was stirred for 30 min. The reaction mixture was then diluted with 300 mL of hexane, washed with 200 mL of a saturated aqueous $NaHCO_3$ solution, 200 mL of a

10 % aqueous $CuSO_4$ solution, 200 mL of H_2O, 200 mL of a saturated aqueous $NaHCO_3$ solution and 200 mL of brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure t give 1.05 g of a yellow solid. The crude mixture was filtered through silica gel with 10% ethyl acetate in hexanes to give 965 mg of a white solid which was further purified by silica gel chromatography eluting with 2% ethyl acetate in hexanes to yield 745 mg (75 %) of ketocarbonate 6 (P_{10} = TES, P_{13} = TBS, R = Et) as a white solid. The product was isolated as a 6:1 ratio of conformational isomers. The following NMR data is for the predominant conformer.

6 (P_{10} = TES, P_{13} = TBS, R = Et): mp 103-104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H, TBS CH_3), 0.08 (s, 3H, TBS CH_3), 0.56 (q, J = 7.8 Hz, 6H, TES CH_2), 0.94 (t, J = 7.8 Hz, 9H, TES CH_3), 0.96 (s, 9H, TBS t-Bu), 1.08 (s, 3H, CH_3 17), 1.29 (m, 1H, H6), 1.38 (s, 3H, CH_3 19), 1.42 (s, 3H, CH_3 16), 1.66 (dd, J = 4.6, 12.5 Hz, 1H, H9α), 1.83 (s, 3H, CH_3 18), 1.85 (dd, J = 4.5, 4.5 Hz, 1H, H14α), 2.05 (m, 1H, H5), 2.06 (dd, J = 6.4, 14.2 Hz, 1H, H5), 2.47 (m, 2H, H9α, H6), 3.01 (dd, J = 3.7, 12.3 Hz, 1H, H14β), 4.20 (m, 2H, H2α, H2β), 4.47 (d, J = 7.3 Hz, 1H, H13β), 4.50 (dd, J = 4.6, 11.4 Hz, 1H, H10β), 4.91 (dd, J = 1.83, 10.1 Hz, 1H, H20), 4.97 (dd, J = 1.8, 16.9 Hz, 1H, H20), 5.29 (dd, J = 0.9, 10.1 Hz, 1H, H7), 5.73 (dddd, J = 6.9, 6.9, 10.5, 16.9 Hz, 1H, H4); ^{13}C NMR δ (ppm) -5.3 (TBS CH_3), -4.5 (TBS CH_3), 4.8 (TES CH_2), 6.5 (TES CH_3), 14.0 (OEt CH_3), 15.5 (CH_3 19), 15.9 (CH_3 18), 18.1 (TBS $\underline{C}(CH_3)_3$), 25.8 (TBS $C(\underline{C}H_3)_3$), 27.6 (CH_3 17), 28.2 (CH_3 16), 30.4, 30.5 (C5, C6), 34.1 (C14), 39.0 (C15), 41.1 (C2), 47.1 (C1), 47.5 (C9), 55.1 (C8), 63.8 (OEt CH2), 66.3 (C13), 68.3 (C10), 84.0 (C7), 114.8 (C20), 134.8 (C11), 138.1 (C4'), 144.9 (C12), 155.7 (Ethylcarbonate C=O), 214.8 (C3); IR (CCl_4) υ 3000, 2950, 2900, 1770, 1700, 1490, 1390, 1280, 1140, 1100, 1030, 910, 880, 860 cm^{-1}; MS (EI) 636 (M, 100), 593 (20), 538 (34), 409 (33); Anal. Calcd. for $C_{35}H_{64}O_6Si_2$: C, 65.99; H, 10.13. Found: C, 65.88, H, 10.17.

Hydroxyketone 7. To a stirred solution of ketocarbonate 6 (P_{10} = TES, P_{13} = TBS, R = Et) (4.00 g, 6.28 mmol) in THF (65 mL) under nitrogen at -35 °C was added 50 mL of a 0.2 M solution (10 mmol) of LDA in THF down the side of the flask over a 10 min period. After 30 min, the reaction mixture was cooled to -78 °C and 2.29 g of (R)-camphorylsulfonyl oxaziridine (10 mmol) in THF (18 mL) was added dropwise down the side of the flask. After 30 min, the reacion mixture was

quenched with 300 mL of a saturated aqueous $NaHCO_3$ solution and extracted with 500 mL and then 150 mL of 25% ethyl acetate in hexanes. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield 7 g of a waxy solid. This material was purified by flash chromatography, eluting with 3% ethyl acetate in hexanes to yield 3.50 g of hydroxyketone 7 (P_{10} = TES, P_{13} = TBS, R = Et) (85%).

7 (P_{10} = TES, P_{13} = TBS, R = Et): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 3H, TBS CH_3), 0.03 (s, 3H, TBS CH_3), 0.50 (q, J = 7.8 Hz, 6H, TES CH_2), 0.87 (t, J = 7.8 Hz, 9H, TES CH_3), 0.90 (s, 9H, TBS t-Bu), 1.03 (s, 3H, CH_3 17), 1.25 (t, J = 7.0 Hz, 3H, OEt CH_3), 1.35 (s, 3H, CH_3 19), 1.40 (m, 1H, H6), 1.41 (s, 3H, CH_3 16), 1.66 (dd, J = 4.6, 12.8 Hz, 1H, H9β), 1.77 (d, J = 1.4 Hz, 3H, CH_3 18), 1.83 (dd, J = 6.0, 14.7 Hz, 1H, H14α), 1.97 (dd, J = 4.1, 8.5 Hz, 1H, H1), 2.02 (m, 2H, H5, H5), 2.44 (dd, J = 11.9, 11.9 Hz, 1H, H9α), 2.75 (d, J = 10.5 Hz, 1H, OH-2), 4.14 (q, J = 14.2 Hz, 2H, OEt CH_2), 4.35 (dd, J = 6.0, 8.7 Hz, 1H, H13), 4.42 (dd, J = 4.6, 11.0 Hz, 1H, H10), 4.49 (dd, J = 4.1, 10.1 Hz, 1H, H2), 4.86 (dd, J = 1.8, 10.3 Hz, 1H, H20), 4.92 (dd, J = 1.8, 16.9 Hz, 1H, H20), 5.23 (dd, J = 1.4, 10.1 Hz, 1H, H7), 5.67 (dddd, J = 6.9, 6.9, 10.5, 16.9 Hz, 1H, H4); ^{13}C NMR δ (ppm) -5.3 (TBS CH_3), -4.5 (TBS CH_3), 4.7 (TES CH_2), 6.5 (TES CH_3), 14.0 (OEt CH_3), 15.0 (CH_3 19), 16.0 (CH_3 18), 18.0 (TBS $\underline{C}(CH_3)_3$), 25.8 (TBS $C(\underline{C}H_3)_3$), 27.5, 27.8 (CH_3 17), 28.1 (CH_3 16), 30.4, 30.5 (C5, C6), 36.9 (C15), 47.3 (C9), 54.5 (C1), 54.7 (C8), 63.9 (OEt CH_2), 66.2 (C13), 67.8 (C10), 70.3 (C2), 83.6 (C7), 114.9 (C20), 135.4(C11), 137.9 (C4'), 144.5 (C12), 155.6 (Ethylcarbonate C=O), 217.8 (C3); IR (CCl_4) υ 3600, 2950, 2900, 1750, 1700, 1660, 1470, 1400, 1370, 1240, 1080, 1050, 1000, 840, 680 cm^{-1}; MS (CI) 653 (M+1, 8), 564 (100), 431 (69), 389 (67).

Hydroxycarbonate 8. To a vigorously stirred solution of hydroxyketone 7 (P_{10} = TES, P_{13} = TBS, R = Et) (2.69 g, 4.12 mmol) in toluene (117 mL) under nitrogen at -78 °C was added dropwise down the side of the flask 85 mL of a 0.97 M solution (82.4 mmol) of RedAl in toluene. After 6 h at -78 °C, the solution was allowed to gradually warm to room temperature over a period of 6 h. The mixture was recooled to -10 °C and 125 mL of a 2 M solution (250 mmol) of acetic acid in THF was added dropwise down the side of the flask. The cloudy mixture was stirred 10

min then poured into 1200 mL of 50% ethyl acetate in hexanes and washed with 1 L of a saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with four 500 mL portions of ethyl acetate and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield 2.29 g of 2,3,7-triol as a white solid. This material was used without further purification.

To a vigorously stirred solution of triol (2.29 g, 3.93 mmol) in CH_2Cl_2 (157 mL) and pyridine (15.7 mL) under nitrogen at -78 °C was quickly added 7.6 mL of a 3.0 M solution (23 mmol) of phosgene in toluene. The solution was allowed to warm to room temperature over a period of 1 h then poured into 250 mL of ethyl acetate, washed with two 125 mL portions of a saturated aqueous $NaHCO_3$ solution and 100 mL brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield 2.52 g yellow oil. This material was filtered through a 2 inch pad of silica gel with 50% ethyl acetate in hexanes and concentration under reduced pressure yielded 2.39 g (95% from 7) of hydroxy carbonate 8 (P_{10} = TES, P_{13} = TBS) as a white solid.

8 (P_{10} = TES, P_{13} = TBS): mp 155 - 157 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H, TBS CH_3), 0.10 (s, 3H, TBS CH_3), 0.59 (q, J = 8.2 Hz, 6H, TES CH_2), 0.96 (t, J = 8.2 Hz, 9H, TES CH_3), 0.97 (s, 9H, TBS t-Bu), 1.11 (s, 3H, CH_3 19), 1.14 (s, 3H, CH_3 17), 1.30 (s, 3H, CH_3 16), 1.39 (dd, J = 4.1, 13.3 Hz, 1H, H9β), 1.65 (m, 2H, H6, H6), 1.99 (dd, J = 6.4, 15.1 Hz, 1H, H14α), 2.01 (d, J = .9 Hz, 3H, CH_3 18), 2.04 (d, J = 3.7 Hz, 1H, H1), 2.11 (ddd, J = 7.8, 15.6, 15.6 Hz, 1H, H5), 2.28 (ddd, J = 9.6, 9.6, 14.2 Hz, 1H, H14β), 2.34 (dd, J = 12.4, 13.3 Hz, 1H, H9β), 2.41 (m, 1H, H5), 3.87 (dd, J = 0.9, 10.5 Hz, 1H, H7), 3.95 (d, J = 3.7 Hz, 1H, H2), 4.59 (dd, J = 3.7, 11.4 Hz, 1H, H10β), 4.40 (s, 1H, H3), 4.55 (dd, J = 6.4, 8.7 Hz, 1H, H13), 5.03 (d, J = 10.5 Hz, 1H, H20), 5.07 (dd, J = 1.5, 17.0 Hz, 1H, H20), 5.77 (m, 1H, H4); ^{13}C NMR δ (ppm) -5.4 (TBS CH_3), -4.4 (TBS CH_3), 4.8 (TES CH_2), 6.5 (TES CH_3), 15.5 (CH_3 18), 17.9 (TBS $\underline{C}(CH_3)_3$), 18.2 (CH_3 19), 25.6 (TBS $C(\underline{C}H_3)_3$), 25.9 (CH_3 16), 27.5 (CH_3 17), 28.3 (C6), 28.4 (C5), 29.8 (C14), 30.8 (C15), 36.5 (C8), 36.8 (C9), 37.3, 50.8 (C1), 66.6 (C10), 67.8 (C13), 70.5 (C2), 91.9 (C3), 91.9 (C7), 116.3 (C20), 133.7 (C11), 137.9 (C4'), 142.6 (C12), 148.0 (cyclic carbonate C=O); IR (CCl_4) υ 3450, 2950, 2870, 1750, 1460, 1380, 1350, 1220, 1120, 1080, 1040, 980, 900, 820, 710 cm^{-1}; MS (CI) 625 (M+1-H_2O, 6), 551 (11), 477 (100), 459 (12), 433 (8), 344 (90); Anal.

Calcd. for $C_{33}H_{60}O_6Si_2$: C, 64.92; H, 9.90; Found: C, 65.13; H, 9.88.

Ketocarbonate 9. To a vigorously stirred solution of dimethylsulfoxide (2.41 mL, 34 mmol) in CH_2Cl_2 (57 mL) under nitrogen at -78 °C was added 8.5 mL of a 2.0 M solution (17.0 mmol) of oxalyl chloride in CH_2Cl_2. After 10 min, a solution of hyroxycarbonate 8 (P_{10} = TES, P_{13} = TBS) (3.45 g, 5.67 mmol) in 16 mL CH_2Cl_2 was added dropwise down the side of the flask. After 30 min at -78 °C, triethylamine (6.8 mL, 49 mmol) was added and the mixture was warmed to room temperature. The mixture was diluted with 200 mL hexanes, washed with two 75 mL portions of a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield 3.45 g of a yellow solid. This material was filtered though a 1 inch pad of silica gel with 10% ethyl acetate in hexanes and then recrystallized from hexanes to yield 2.62 g of ketocarbonate 9 as white crystals. The mother liquor was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexanes and then recrystallization from hexanes to yield an additional 0.58 g of ketocarbonate 9 (P_{10} = TES, P_{13} = TBS) (total yield: 3.20 g, 93%).

9 (P_{10} = TES, P_{13} = TBS): mp 140.0 - 141.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 3H, TBS CH_3), 0.12 (s, 3H, TBS CH_3), 0.60 (q, J = 7.8 Hz, 6H, TES CH_2), 0.96 (t, J = 7.8 Hz, 9H, TES CH_3), 0.98 (s, 9H, TBS t-Bu), 1.06 (s, 3H, CH_3 19), 1.17 (s, 6H, CH_3 16, CH_3 19), 1.42 (dd, J = 3.7, 14.2 Hz, 1H, H9β), 1.63 (m, 2H, H6, H6), 2.12 (m, 1H, H5), 2.38 (d, J = 0.9 Hz, 3H, CH_3 18), 2.47 (dd, J = 11.4, 13.3 Hz, 1H, H9α), 2.65 (d, J = 8.2, 1H, H1), 3.94 (dd, J = 1.4, 10.4 Hz, 1H, H7), 4.44 (dd, J = 3.7, 11.4 Hz, 1H, H10), 4.49 (s, 1H, H3), 4.64 (dd, J = 6.9, 7.8 Hz, 1H, H13), 5.04 (dd, J = 1.4, 11.9 Hz, 1H, H20), 5.07 (dd, J = 1.8, 17.4 Hz, 1H, H20), 5.76 (m, 1H, H4); ^{13}C NMR δ (ppm) -5.4 (TBS CH_3), -4.5 (TBS CH_3), 4.8 (TES CH_2), 6.5 (TES CH_3), 15.7 (CH_3 18), 17.8 (CH_3 19), 17.9 (TBS $\underline{C}(CH_3)_3$), 25.5 (TBS $C(\underline{C}H_3)_3$), 28.2 (CH_3 16), 28.3 (CH_3 17), 28.3 (C6), 29.6 (C5), 30.4 (C14), 37.7 (C15), 38.0 (C8, C9), 62.1 (C1), 66.5 (C10), 67.5 (C13), 91.3 (C3), 91.5 (C7), 116.4 (C20), 132.8 (C11), 137.0 (C4'), 145.4 (C12), 146.6 (cyclic carbonate C=O), 206.8 (C2); IR (CCl_4) υ 2930, 2860, 1760, 1670, 1450, 1380, 1340, 1240, 1180, 1170, 1120, 1090, 1060, 1040, 980, 890, 860, 820, 700, 650 cm^{-1}; MS (CI) 607 (M+1, 6), 549 (11), 475 (100), 431 (4), 347 (45);

Anal. Calcd. for $C_{33}H_{58}O_6Si_2$: C, 65.30; H, 9.63; Found: C, 65.23; H, 9.66.

2-Keto-3-Hydroxy-Lactone 10. To a stirred solution of 3,7-cyclic carbonate 9 (P_{10} = TES, P_{13} = TBS) (2.246 g, 3.70 mmol) in THF (9 mL) was added 19.4 mL of 0.2 M LTMP (3.88 mmol) in THF dropwise down the sides of the flask at -25 °C. The reaction mixture was allowed to warm to -10 °C over the course of 30 min. The cold reaction mixture was poured into 100 mL of 10% aqueous acetic acid and extracted with 100 mL of 10 % ethyl acetate in hexanes. The organic phase was washed with 50 mL of a saturated aqueoues $NaHCO_3$ solution and 50 mL of brine. The combined aqueous phases were extracted with two 20 mL portions of 10% ethyl acetate in hexanes. The oraganic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2.4 g of a yellow oil. This material was purified by silica gel chromatography, eluting with 5% then 10% ethyl acetate in hexanes to yield 2.033 g (90%) of the hydroxy lactone 10 (P_{10} = TES, P_{13} = TBS) as a foamy solid and 0.207 g (7.2%) of the 3-carbamate.

10 (P_{10} = TES, P_{13} = TBS): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 3H, TBS CH_3), 0.14 (s, 3H, TBS CH_3), 0.61 (q, J = 7.8 Hz, 6H, TES CH_2), 0.92 (s, 9H, TBS t-Bu), 0.97 (t, J = 7.8 Hz, 9H, TES CH_3), 1.11 (s, 3H, CH_3 17), 1.22 (s, 3H, CH_3 19), 1.27 (s, 3H, CH_3 16), 1.32 (dd, J = 3.2, 13.3 Hz, 1H, H9β), 1.64 (ddd, J = 2.3, 6.9, 9.2 Hz, 1H, H6), 2.07 (m, 2H, H6, H5), 2.17 (m, 1H, H14α), 2.33 (m, 1H, H5), 2.65 (m, 2H, H14β, H1), 2.74 (dd, J = 12.4, 12.4 Hz, 1H, H9α), 3.92 (dd, J = 2.8, 11.5 Hz, 1H, H7), 4.47 (dd, J = 3.2, 11.0 Hz, 1H, H10), 4.55 (dd, J = 2.8, 9.6 Hz, 1H, H13), 5.02 (d, J = 10.1 Hz, 1H, H20), 5.07 (dd, J = 1.4, 16.9 Hz, 1H, H20), 5.81 (dddd, J = 6.9, 6.9, 10.5, 16.9 Hz, 1H, H4); ^{13}C NMR δ (ppm) -5.2 (TBS CH_3), -4.5 (TBS CH_3), 4.8 (TES CH_2), 6.6 (TES CH_3), 16.4 (CH_3 18), 17.9 (TBS $\underline{C}(CH_3)_3$), 24.2 (CH_3 19), 25.7 (TBS $C(\underline{C}H_3)_3$), 26.9 (CH_3 16), 30.1 (CH_3 17), 30.4 (C5), 32.7 (C6), 32.9 (C14), 39.1 (C15), 40.6 (C9), 48.1 (C8), 62.0 (C1), 67.3 (C10), 67.6 (C13), 87.9 (C3), 91.1 (C7), 115.8 (C20), 137.7 (C11), 138.5 (C4'), 143.0 (C12), 173.5 (C4), 207.6 (C2); IR (CCl_4) υ 3500, 2970, 2900, 1780, 1700, 1480, 1360, 1260, 1210, 1160, 1070, 1010, 910, 890, 840 cm^{-1}; MS (EI) 606 (M, 100), 549 (69), 474 (27), 431 (65), 417(40); Anal. Calcd. for $C_{33}H_{58}O_6Si_2$: C, 65.30; H, 9.63; Found: C, 65.38; H, 9.64.

Keto Lactone **11**. To the 2-keto-3-hydroxylactone **10** (P_{10} = TES, P_{13} = TBS) (1.10 g, 1.83 mmol) was added a 0.1 M solution of SmI_2 in THF (82 mL, 8.2 mmol). The resulting dark blue solution was stirred at room temperature under N_2 for 4h. After cooling to 0 °C an ethereal solution of HCl (0.66M; 4.2 mL, 2.77 mmol) was added; after 5 min the flask was opened to the air and the reaction mixture was diluted with 200 mL of cold ethyl acetate, then poured into 50 mL of ice cold 0.2N aqueous HCl. The organic phase was separated and washed with 50 mL of a 5% aqueous citric acid solution, two 50 mL portions of a saturated aqueous $NaHCO_3$ solution and 50 mL of brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting material was dissolved in 100 mL of hexanes, then silica gel (230-400 mesh; 4.3 g) was added and the mixture was vigorously stirred at room temperature for 65 min before filtering through a 1 inch pad of silica gel eluting with 300 mL of 20% ethyl acetate in hexanes. The solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexanes to yield 822 mg (77%) of the *cis*-ketolactone **11** and 164 mg (15%) of the corresponding *trans* isomer.

To a solution of the *trans*-2-ketolactone (611 mg, 1.03 mmol) stirred in 10 mL of THF under nitrogen at 0 °C was added down the side of the flask 6.8 mL of a 0.6 M solution (4.1 mmol) of t-BuOK in THF. The resulting solution was stirred for 1.5 h then 10 mL of a 10% acetic acid solution in THF was added down the side of the flask. After stirring for 5 min the mixture was diluted with 200 mL of hexanes and poured into 100 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was washed with water and brine then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield 615 mg of pale brown oil. The oil was dissolved in 10 mL of hexanes and silica gel (3.0 g) was added. The mixture was stirred vigorously for 15 min then filtered through a 1/2 in plug of silica gel with 20% ethyl acetate in hexanes. Concentration of the filtrate under reduced pressure yielded 576 mg of pale yellow oil. This material was purified by silica gel chromatography, eluting with 10% then 20% ethyl acetate in hexanes to yield 472 mg (77%) of pure *cis*-2-ketolactone **11** (P_{10} = TES, P_{13} = TBS), 84 mg (13%) of pure *trans* isomer and 24 mg of a 6:1 mixture of *cis*:*trans* isomers.

11 (P_{10} = TES, P_{13} = TBS): mp = 86.5 - 88.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H,

TBS CH_3), 0.07 (s, 3H, TBS CH_3), 0.54 (q, J = 7.8 Hz, 6H, TES CH_2), 0.84 (s, 9H, TBS t-Bu), 0.90 (t, J = 7.8 Hz, 9H, TES CH_3), 1.03 (s, 3H, CH_3 17), 1.11 (s, 3H, CH_3 16), 1.15 (s, 3H, CH_3 19), 1.35 (dddd, J = 4.6, 4.6, 7.3, 14.2 Hz, 1H, H6), 1.43 (dd, J = 3.7, 12.8 Hz, 1H, H9β,), 1.67 (dddd, J = 3.2, 7.3, 10.1, 13.7 Hz, 1H, H6), 1.83 (dd, J = 4.6, 16.0 Hz, 1H, H14α), 2.03 (m, 1H, H5), 2.07 (d, J = 1.4 Hz, 3H, CH_3 18), 2.25 (m, 1H, H5), 2.30 (dd, J = 11.9, 12.3 Hz, 1H, H9α), 2.45 (d, J = 8.2 Hz, 1H, H1), 2.58 (ddd, J = 8.7, 9.2, 16.0 Hz, 1H, H14β), 3.93 (dd, J = 2.8, 11.4 Hz, 1H H7β), 4.03 (s, 1H, H3α), 4.37 (dd, J = 3.7, 11.0 Hz, 1H, H10β), 4.46 (ddd, J = 1.4, 4.6, 9.2 Hz, 1H, H13β), 4.96 (dd, J = 1.4, 10.1 Hz, 1H, H20), 5.01 (dd, J = 1.4, 17.4 Hz, 1H, H20), 5.73 (dddd, J = 6.4, 7.3, 10.5, 16.9 Hz, 1H, H4); ^{13}C NMR δ (ppm) -5.3 (TBS CH_3), -4.6 (TBS CH_3), 4.5 (TES CH_2), 6.5 (TES CH_3), 15.0 (CH_3 18), 18.0 (TBS $\underline{C}(CH_3)_3$), 25.7 (TBS $C(\underline{C}H_3)_3$), 28.9 (CH_3 19), 29.2 (CH_3 16), 29.8 (C5), 29.9 (CH_3 17), 30.3 (C6), 32.8 (C14), 38.5 (C15), 44.2 (C8), 44.9 (C9), 60.6 (C3), 61.2 (C1), 66.9 (C10), 67.8 (C13), 91.9 (C7), 115.7 (C20), 137.7 (C11), 138.5 (C4'), 142.4 (C12), 174.7 (C4), 204.8 (C2); IR (CCl_4) υ 2975, 2899, 1780, 1705, 1460, 1355, 1260, 1180, 1070, 1060, 1000, 830 cm^{-1}; MS (CI) 591 (M+1, 5), 523 (6), 459(100), 441 (5); Anal. Calcd. for $C_{33}H_{58}O_5Si_2$: C, 66.07; H, 9.89; Found: C, 66.97; H, 9.91.

1-Hydroxy-2-Keto-Lactone 12. To 34.2 mL of a stirred 0.2 M solution (6.84 mmol) of LTMP in THF under nitrogen at -10 °C was added a solution of ketolactone 11 (P_{10} = TES, P_{13} = TBS) (1.008 g, 1.71 mmol) in 10 mL of THF dropwise down the side of the flask. After 0.5 h, the reaction mixture was cooled to -40 °C and a solution of (±)-camphorsulfonyl oxaziridine (1.96 g, 8.55 mmol) in THF (10 mL) was added dropwise down the side of the flask. After 20 min, the reaction mixture was cooled to -78 °C, diluted with 200 mL of hexanes and rapidly poured into 250 mL of a vigorously stirred saturated aqueous NH_4Cl solution. The aqueous phase was extracted with two 50 mL portions of hexane and the combined organic phase were dried over anhydrous Na_2SO_4 and concetrated under reduced pressure to give 1.4 g of a waxy solid. This material was chromatographed (CH_2Cl_2 followed by hexanes increasing to 10% ethyl acetate in hexanes) to give 0.882 g of hydroxyketolactone 12 (P_{10} = TES, P_{13} = TBS) (85%) as a white solid, 0.083 g of the corresponding *trans*-hydroxyketolactone (8 %) as a solid, and 31 mg of

returned ketolactone 11 (3 %).

12 (P_{10} = TES, P_{13} = TBS): mp 124-126 °C; 1H NMR (C_6D_6) δ (ppm) 0.09 (s, 3H, CH_3 in TBDMS), 0.17 (s, 3H, CH_3 in TBDMS), 0.62 (q, J = 7.78 Hz, 6H CH_2's in TES), 1.03 (t, J =7.78, 9H CH_3's in TES), 1.05 (s, 3H, $CH_3$19), 1.13 (s, 9H, t-Bu in TBS), 1.20 (s, 3H, $CH_3$17), 1.39 (m, 1H, H6), 1.42 (s, 3H, $CH_3$16), 1.44 (dd, J = 0.92, 13.28 Hz, 1H, H9β), 1.98 (dd, J = 9.61, 12.82 Hz, 1H, H14β), 2.05 (m, 1H, H5), 2.06 (broad, 1H, OH1, D2O exchangable), 2.25 (m, 1H, H6), 2.27 (d, J = 0.91 Hz, 3H, $CH_3$18), 2.29 (m, 1H, H5), 2.41 (dd, J = 10.98, 13.28 Hz, 1H, H9α), 2.56 (dd, J = 3.21, 12.82 Hz, 1H, H14α), 3.83 (dd, J = 2.75, 11.90 Hz, 1H, H7), 4.04 (s, 1H, H3), 4.47 (dd, J = 0.92, 10.98 Hz, 1H, H10), 4.60 (ddq, J = 0.91, 3.21, 9.61 Hz, 1H, H13), 5.11 (br d, J = 10.53 Hz, 1H, H20), 5.18 (br d, J = 17.40 Hz, 1H, H20), 5.77 (m, 1H, H4); 13C NMR ($CDCl_3$) δ (ppm) -5.4 (TBS CH_3), -4.7 (TBS CH_3), 4.5 (TES CH_2), 6.5 (TES CH_3), 15.5 (CH_3 18), 17.9 (TBS $\underline{C}(CH_3)_3$), 22.5 (CH_3 19), 25.7 (TBS $C(\underline{C}H_3)_3$), 26.3 (CH_3 16), 29.8 (CH_3 17), 29.8 (C5), 30.4 (C6), 39.6 (C14), 41.3 (C15), 44.5 (C9), 45.0 (C8), 58.1 (C3), 66.5 (C10), 68.2 (C13), 83.0 (C1), 91.7 (C7), 115.7 (C20), 137.0 (C11), 137.6 (C4'), 145.5 (C12), 175.0 (C4), 202.4 (C2); IR (CCl4) υ 3500, 3000, 1780, 1720, 1100 cm^{-1}; MS (CI) 607 (M+1, 10), 589 (56), 475 (100), 457 (61); Anal. Calcd for $C_{33}H_{58}O_6Si_2$: C, 65.30; H, 9.63. Found: C, 65.19; H, 9.60.

1,2-Dihydroxy-trans-lactone 13. To a stirred 1.23 M solution of Red-Al (4.6 mmol, 5.6 mmol) in THF under nitrogen at -78 °C was quickly added a solution of *cis*-hydroxyketone 12 (P_{10} = TES, P_{13} = TBS) (342 mg, 0.563 mmol) in THF (25 mL). After 1.5 h, 25 mL of a 15 % aqueous NaOH solution was added dropwise directly to the reaction mixture. The reaction mixture was vigorously stirred at room temperature for 3 h and was then poured into 100 mL of H_2O and extracted with two 100 mL portions of ether. The organic phases were combined and washed with 100 mL of H_2O and 100 mL of brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 0.35 g of a pale yellow solid. This material was purified by silica gel chromatography eluting with 10% ether in hexanes followed by 25% ethyl acetate in hexanes to yield 290 mg *trans*-diol 13 as colorless needles, 14.5 mg (4.2 %) of trans-hydroxyketone, and 20 mg of a mixture of *cis*-diol and unknown byproducts. To a solution of the mixture containing *cis*-

diol in THF (1 mL) under nitrogen at room temperature was added 0.5 mL a 30% aqueous solution of NaOH. After 2.5 h, the reaction mixture was poured into 30 mL of H_2O and extracted with 30 mL of ether. The organic phase was washed with 30 mL of H_2O and 30 mL of brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 0.02 g of a yellow solid, which was purified by silica gel chromatography eluting with 5% ethyl acetate in hexanes to yield an additional 12 mg (total yield: 302 mg, 88%) of *trans*-diol 13 (P_{10} = TES, P_{13} = TBS).

13 (P_{10} = TES, P_{13} = TBS): mp 127-128°C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H, TBS CH_3), 0.11 (s, 3H, TBS CH_3), 0.60 (q, J = 8.1 Hz, 6H, TES CH_2), 0.87 (s, 9H, TBS t-Bu), 0.96 (t, J = 8.1 Hz, 9H, TES CH_3) 1.13 (s, 3H, CH_3 17), 1.23 (s, 3H, CH_3 16), 1.31 (s, 3H, CH_3 19), 1.42 (dd, J = 3.7, 12.8 Hz, 1H, H9β), 1.46 (ddd, J = 4.8, 8.8, 11.4 Hz, 1H, H6), 1.74 (dddd, J = 3.3, 7.3, 9.9, 12.4 Hz, 1H, H6), 1.99 (d, J = 1.5 Hz, 3H, CH_3 18), 2.10 (m, 1H, H5), 2.21 (dd, J = 3.7, 5.4 Hz, 1H, H14α), 2.26 (m, 3H, H5, H9α, H14β), 2.92 (d, J = 7.7 Hz, 1H, H3), 3.84 (dd, J = 2.2, 7.7 Hz, 1H, H2), 3.85 (s, 1H, OH1), 3.97 (dd, J = 2.9, 11.4 Hz, 1H, H7), 4.47 (dd, J = 3.7, 11.4 Hz, 2H, H13, H10), 5.01 (dd, J = 1.8, 12.2 Hz, 1H, H20), 5.07 (dd, J = 1.7, 17.0 Hz, 1H, H20), 5.78 (dddd, J = 7.3, 7.3, 10.1, 16.5 Hz, 1H, H4), 6.87 (d, J = 2.9 Hz, 1H, OH2), ^{13}C NMR ($CDCl_3$) δ (ppm) -5.31, -4.59, 4.79, 6.55, 16.60, 17.68, 21.24, 24.70, 25.62, 28.50, 29.52, 30.05, 40.20, 40.41, 44.18, 45.18, 45.60, 66.62, 69.25, 71.32, 88.91, 116.09, 136.96, 138.63, 139.93, 180.10, IR ($CHCl_3$) υ 3050, 1730, 1460, 1350 cm^{-1}, MS (EI) 608 (M, 13), 590 (26), 267 (100), Anal. Calcd. for $C_{33}H_{60}O_6Si_2$: C, 65.08; H, 9.92. Found C, 65.06; H, 9.98.

Carbonate 14. To a stirred solution of diol 13 (P_{10} = TES, P_{13} = TBS) (1.00 g, 1.64 mmol) in CH_2Cl_2 (58 mL) and pyridine (5.8 mL) under nitrogen at -78 °C was added dropwise 8.2 mL of 2 M solution (16.4 mmol) of phosgene in toluene. Then the reaction mixure was warmed to -23 °C and stirred for 30 min. To the resulting mixture, 50 mL of a saturated aqueous $NaHCO_3$ solution was added. After warming to room temperature for 10 min, the reaction mixture was extracted with 200 mL of 10% ethyl acetate in hexanes. The organic phase was washed with 100 mL of a 10 % aqueous $CuSO_4$ solution, two 200 mL portions of a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 1.1 g of a

pale yellow solid. This material was filtered through a 3 inch pad of silica gel with 15% ethyl acetate in hexanes to yield 1.045 g (100%) of carbonate **14** (P_{10} = TES, P_{13} = TBS) as a white solid.

14 (P_{10} = TES, P_{13} = TBS): mp 146-147 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 3H, TBS CH_3), 0.12 (s, 3H, TBS CH_3), 0.61 (q, J = 7.8 Hz, 6H, TES CH_2), 0.88 (s, 9H, TBS t-Bu), 0.96 (t, J = 7.8 Hz, 9H TES CH_3), 1.20 (s, 3H, CH_3 17), 1.30 (s, 3H, CH_3 16), 1.32 (s, 3H, CH_3 19), 1.40 (ddd, J = 2.7, 4.5, 9.2 Hz, 1H, H6), 1.44 (d, J = 3.7, 13.3 Hz, 1H, H9β), 1.71 (dddd, J = 2.7, 6.9, 9.6, 12.8 Hz, 1H, H6), 2.11 (ddd, J = 7.8, 15.3, 15.3 Hz, 1H, H5), 2.29 (dd, J = 3.2, 15.6 Hz, 1H, H14α), 2.31 (m, 2H, H5, H9α), 2.59 (dd, J = 9.2, 15.6 Hz, 1H, H14β), 2.99 (d, J = 7.3 Hz, 1H, H3α), 4.02 (dd, J = 2.7, 11.4 Hz, 1H, H7β), 4.38 (dd, J = 3.7, 11.0 Hz, 1H, H10β), 4.47 (d, J = 7.3 Hz, 1H, H2β), 4.57 (dd, J = 2.1, 9.2 Hz, 1H, H13β), 5.02 (dd, J = 1.4, 10.1 Hz, 1H, H20), 5.06 (dd, J = 1.4, 16.9 Hz, 1H, H20), 5.77 (dddd, J = 6.9, 6.9, 10.1, 17.0 Hz, 1H, H4), ^{13}C NMR ($CDCl_3$) δ (ppm) -5.37, -4.60, 4.75, 6.51, 17.02, 17.60, 21.24, 24.64, 25.55, 27.36, 29.50, 30.11, 37.56, 39.96, 42.89, 43.75, 45.39, 66.54, 68.29, 87.37, 90.05, 116.15, 136.54, 136.94, 144.93, 153.32, 169.89, IR ($CHCl_3$) υ 3070, 1800 cm^{-1}, MS (EI) 634 (M, 12), 577 (100), Anal. Calcd. for $C_{34}H_{58}O_7Si_2$: C, 64.31; H, 9.21. Found C, 64.41; H, 9.22.

Ketoester **15**. To a stirred solution of lactone **14** (P_{10} = TES, P_{13} = TBS) (1.05g, 1.65 mmol) in methanol (70 mL) under nitrogen at -78 °C was added a saturated solution of ozone in methylene chloride (50 mL, 40 mL then 8 mL) until no more starting material remained by TLC analysis. Triethylamine (4.8 mL) and trimethylphosphite (3.1 mL) were added sequentially to the resulting mixture at -78 °C. After stirring 5 min, the solution was warmed to 0 °C and stirred for 2 h. The resulting solution was poured into 250 mL of a saturated aqueous $NaHCO_3$ solution and extacted with three 200 mL portions of CH_2Cl_2. The combined organic layers were washed with 150 mL of a saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 1.10 g of the aldehyde as a colorless oil. This material was used further purification.

To a stirred solution of the aldehyde (1.10 g) in t-butanol (30.8 mL), acetone (10.3 mL) and 8 mL

of a 1.25 M (10 mmol) aqueous KH_2PO_4 solution at 0 °C was added 11.3 mL of a 1 M (11.3 mmol) aqueous $KMnO_4$ solution over the course of 2 min. The reaction mixture was stirred at 0 °C for 30 min, poured into 200 mL of a 10% aqueous $Na_2S_2O_3$ solution and extracted with three 200 mL portions of ethyl acetate. The combined organic layers were washed with 50 mL of water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. To a stirred solution of the oily residue in ether (30 mL) at room temperature was added an ethereal solution of CH_2N_2 (20 mL). The solution was concentrated under reduced pressure to give 1.15 g of a colorless oil. This material was filtered through a 2 inch pad of silica gel with 40% ethyl acetate in hexanes and concentration under reduced pressure yielded 1.01 g (91%) of lactone ester **15** (P_{10} = TES, P_{13} = TBS, R = Me).

15 (P_{10} = TES, P_{13} = TBS, R = Me): ^1H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 3H, TBS CH_3), 0.12 (s, 3H, TBS CH_3), 0.60 (q, J = 8.1 Hz, 6H, TES CH_2), 0.88 (s, 9H, TBS t-Bu), 0.96 (t, J = 8.1 Hz, 9H, TES CH_3), 1.21 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.51 (dd, J = 3.7, 13.2 Hz, 1H, H9β), 1.53 (m, 1H, H6), 2.06 (d, J = 1.1 Hz, 3H, CH_3 18), 2.07 (ddd, J = 2.9, 7.7, 21.6 Hz, 1H, H6), 2.29 (dd, J = 3.7, 15.8 Hz, 1H, H14α), 2.31 (dd, J = 13.2, 13.2 Hz, 1H, H9α), 2.46 (ddd, J = 7.7, 16.8, 24.5 Hz, 1H, H5), 2.53 (ddd, J = 5.5, 7.7, 16.8 Hz, 1H, H5), 2.60 (dd, J = 9.2, 15.8 Hz, 1H, H14β), 2.99 (d, J = 7.3 Hz, 1H, H3α), 3.68 (s, 3H, CO_2Me), 4.09 (dd, J = 2.6, 12.1 Hz, 1H, H7β), 4.39 (dd, J = 3.7, 11.0 Hz, 1H, H10β), 4.47 (d, J = 7.3 Hz, 1H, H2β), 4.59 (dd, J = 1.8, 9.2 Hz, 1H, H13β); Anal. Calcd. for $C_{34}H_{58}O_9Si_2$: C, 61.22; H, 8.77. Found C, 61.30; H, 8.79.

Enol ester **16**. To a stirred solution of lactone ester **15** (P_{10} = TES, P_{13} = TBS, R = Me) (1.01 g, 1.51 mmol) in THF (24.5 mL) at -78 °C was added slowly a 19.4 mL of a 0.2 M solution (3.88 mmol) of LDA in THF down the side of the flask over the course of 3 min. After stirring 35 min, 10 mL of a 33% solution of acetic acid in THF was quickly added. After 5 min, the mixture was poured into 150 mL of a saturated aqueous $NaHCO_3$ solution and extracted with three 200 mL portions of $CHCl_3$. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 1.02 g of crude enol ester **16** (P_{10} = TES, P_{13} = TBS, R = Me) as a colorless oil. Approximately 3% of unreacted ester lactone **15** was still present

but this material was used without further purification.

16 (P_{10} = TES, P_{13} = TBS, R = Me): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3H, TBS CH_3), 0.10 (s, 3H, TBS CH_3), 0.61 (q, 6H, TES CH_2), 0.87 (s, 9H, TBS t-Bu), 0.96 (t, J = 8.0 Hz, TES CH_3), 1.08 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.33 (S, 3H, CH_3), 1.61 (d, J = 4.3 Hz, 1H, OH-7), 1.89 (dd, J = 4.3, 13.9 Hz, 1H, H9α), 1.95 (dd, J = 11.2, 11.2 Hz, 1H, H9β), 2.01 (d, J = 1.1 Hz, 3H, CH_3 18), 2.22 (ddd, J = 2.7, 10.7, 15.5 Hz, 1H, H6β), 2.45 (dd, J = 4.8, 15.5 Hz, 1H, H6α), 2.54 (dd, J = 9.1, 15.0 Hz, 1H, H14β), 2.86 (dd, J = 3.7, 15.0 Hz, 1H, H14α), 3.07 (s, 1H, H3α), 3.40 (ddd, J = 4.8, 4.8, 9.6 Hz, 1H, H7α), 3.75 (s, 3H, CO_2Me), 4.39 (dd, J = 4.3, 11.2 Hz, 1H, H10β), 4.60 (d, J = 4.3, 11.2 Hz, 1H, H2β), 4.67 (dd, J = 2.1, 9.1 Hz, 1H, H13β), 12.24 (s, 1H, OH4).

Enol ester 17. To a stirred solution of crude enol ester 16 (P_{10} = TES, P_{13} = TBS, R = Me) (1.02 g) in THF (13 mL) and 2-methoxypropene (13 mL) under nitrogen at 0 °C was added 0.48 mL of a 0.1 M solution (0.048 mmol) of p-toluenesulfonic acid in THF. The mixture was stirred at 0 °C for 10 min and then triethylamine (0.66 mL) was added. The mixture was concentrated under reduced pressure and purified by silica gel chromatography, eluting with 7.5% ethyl acetate in hexanes increasing to 30% ethyl acetate in hexanes to yield 938 mg enol ester 17 (P_7 = MOP, P_{10} = TES, P_{13} = TBS, R = Me) (84% from 15) and 30 mg (3%) of recovered lactone ester 15.

17 (P_7 = MOP, P_{10} = TES, P_{13} = TBS, R = Me): mp 95-97 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 3H, TBS CH_3), 0.10 (s, 3H, TBS CH_3), 0.59 (q, J = 7.7 Hz, 6H, TES CH_3), 0.87 (s, 9H, TBS t-Bu), 0.95 (t, J = 7.7 Hz, 9H, TES CH_3), 1.10 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.34 (s, 3H, MOP CH_3), 1.37 (s, 3H, MOP CH_3), 1.84 (m, 2H, H9α, H9β), 1.98 (s, 3H, CH_3 18), 2.17 (ddd, J = 2.8, 10.4, 15.9 Hz, 1H, H6β), 2.52, (dd, J = 9.3, 15.4 Hz, 1H, H14β), 2.63 (dd, J = 4.4, 15.9 Hz, 1H, H6α), 2.88 (dd, J = 3.8, 15.4 Hz, 1H, H14α), 3.06 (s, 1H, H3α), 3.26 (s, 3H, MOP OMe), 3.37 (dd, J = 4.4, 10.4 Hz, 1H, H7α), 3.72 (s, 3H, CO_2Me), 4.36 (dd, J = 6.0, 9.3 Hz, 1H, H10β), 4.57 (d, J = 2.2 Hz, 1H, H2β), 4.67 (dd, J = 2.8, 9.3 Hz, 1H, H13β), 12.24 (s, 1H, OH4).

Enol ester 17 (P_7 = TES). To a solution of the enol ester 16 (P_{10} = TES, P_{13} = TBS, R = Me) (9

mg, 0.0137 mmole) and DMAP (3.5 mg, 0.0286 mmole) in pyridine (0.6 mL) at 0 °C was added triethylsilyl chloride (0.025 mL, 0.14 mmole). The solution was stirred at room temperature for 16 h, diluted with ethyl acetate (10 mL), poured into a saturated aqueous sodium bicarbonate solution (20 mL) and extracted with 20% ethyl acetate/hexane (20 mL x 3). The combined organic layer was dried over anhydrous $NaSO_4$, filtered and concentrated to yield 25 mg of crude **17**. Column chromatography (10% ethyl acetate/ hexane) provided 10 mg (95%) of pure enol ester **17** ($P_7 = P_{10}$ = TES, P_{13} = TBS, R = Me).

17 ($P_7 = P_{10}$ = TES, P_{13} = TBS, R = Me): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 3H, TBS CH_3), 0.10 (s, 3H, TBS CH_3), 0.59 (q, J = 8.1 Hz, 12H, TES CH_2), 0.87 (s, 9H, TBS t-Bu), 0.95 (t, J = 7.7 Hz, 18H, TES CH_3), 1.05 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.84 (m, 2H, H9α, H9β), 1.98 (s, 3H, CH_3 18), 2.17 (ddd, J = 2.8, 10.4, 15.9 Hz, 1H, H6β), 2.31 (dd, J = 4.4, 15.9 Hz, 1H, H6α), 2.52, (dd, J = 9.3, 15.4 Hz, 1H, H14β), 2.85 (dd, J = 3.8, 15.4 Hz, 1H, H14α), 3.03 (br s, 1H, H3α), 3.34 (dd, J = 5.0, 10.4 Hz, 1H, H7α), 3.75 (s, 3H, CO_2Me OMe), 4.36 (dd, J = 5.0, 10.4 Hz, 1H, H10β), 4.58 (d, J = 2.7 Hz, 1H, H2β), 4.66 (br d, J = 11.0 Hz, 1H, H13β), 12.22 (s, 1H, OH4).

Ketone **18**. To a stirred solution of enol ester **17** (P_7 = MOP, P_{10} = TES, P_{13} = TBS, R = Me) (963 mg, 1.3 mmol) in DMF (30 mL) under nitrogen at room temperature was added solid potassium thiophenoxide (250 mg, 1.69 mmol) followed by thiophenol (0.4 mL, 3.9 mmol). The solution was warmed to 86 °C for 3.5 hours. The solution was allowed to cool to room temperature then was poured directly into 250 mL of a saturated aqueous $NaHCO_3$ solution and extracted with three 150 mL portions of 30% ethyl acetate in hexanes. The combined organic phases were then filtered through a 2 inch silica gel pad and subsequently concentrated under reduced pressure to yield 1.29 g of crude product. This material was purified by radial chromatography, eluting with 15% then 20% and finally 25% ethyl acetate in hexanes to yield 763 mg (86%) of ketone **18** (P_7 = MOP, P_{10} = TES, P_{13} = TBS).

18 (P_7 = MOP, P_{10} = TES, P_{13} = TBS): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 3H, TBS CH_3), 0.14 (s, 3H, TBS CH_3), 0.58 (q, J = 8.2 Hz, 6H, TES CH_2), 0.94 (s, 9H, TBS t-Bu), 0.95 (t, J = 8.2 Hz, 9H, TES CH_3), 1.22 (s, 3H, CH_3 19), 1.30 (s, 3H, CH_3 17), 1.32 (s, 6H,

MOP CH_3), 1.33 (s, 3H, CH_3 16), 1.80 (m, 1H, H5), 1.81 (dd, J = 3.8, 3.8 Hz, 1H, H9β), 1.98 (m, 1H, H5), 1.99 (d, J = 1.1 Hz, 3H, CH_3 18), 2.21 (m, 1H, H6β), 2.29 (dd, J = 10.4, 12.1 Hz, 1H, H9α), 2.43 (dd, J = 9.3, 15.4 Hz, 1H, H14α), 2.53 (m, 1H, H6α), 2.63 (dd, J = 5.0, 15.4 Hz, 1H, H14β), 2.70 (d, J = 5.0 Hz, 1H, H3), 3.20 (s, 3H, MOP OMe), 3.39 (dd, J = 6.1, 10.4 Hz, 1H, H7), 4.34 (dd, J = 3.9, 10.4 Hz, 1H, H10), 4.55 (d, J = 5.5 Hz, 1H, H2), 4.73 (dd, J = 5.3, 7.7 Hz, 1H, H13). Anal. Calcd. for $C_{36}H_{64}O_8Si_2$: C, 63.49; H, 9.47. Found C, 63.56; H, 9.55.

18 (P_7= P_{10} = TES, P_{13} = TBS): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 3H, TBS CH_3), 0.14 (s, 3H, TBS CH_3), 0.47-0.63 (m, 12H, TES CH_2), 0.90-0.99 (m, 27H, TBS t-Bu, TES CH_3), 1.22 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.75 (dt, J = 11.6, 1.6 Hz, 1H), 1.85 (d, J = 3.3 Hz, 1H), 1.90 (t, J = 3.9 Hz, 1H), 1.97 (t, J = 8.1 Hz, 1H), 2.00 (s, 3H, CH_3), 2.30 (m, 1H), 2.39-2.60 (m, 3H), 2.65 (m, 1H), 3.35 (dd, J = 9.6, 7.8 Hz, 1H, H7α), 4.35 (dd, J =10.8, 3.3 Hz, 1H, H10β), 4.57 (d, J = 5.1 Hz, 1H, H2β), 4.72 (m, 1H, H13β).

Ketone **18** (P_7=BOM). To a stirred solution of ketone **18** (P_7 = MOP, P_{10} = TES, P_{13} = TBS) (293 mg, 0.43 mmol) in THF (28.6 mL) and methanol (9.5 mL) under nitrogen at room temperature was added dropwise 0.20 mL of a 0.1 M solution of PPTS in CH_2Cl_2 (0.02 mmol). The reaction mixture was stirred for 3 h, poured into 100 mL of a saturated aqueous $NaHCO_3$ solution and extracted with two 100 mL portions of ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield 274 mg of the hydroxy ketone **18** (P_7=H) as a colorless oil. This material was used without further purification.

18 (P_7=H, P_{10} = TES, P_{13} = TBS): mp 75-77 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 3H, TBS CH_3), 0.13 (s, 3H, TBS CH_3), 0.61 (q, J = 8.2 Hz, 6H, TES CH_2), 0.93 (s, 9H, TBS t-Bu), 0.95 (t, J = 7.7 Hz, 9H, TES CH_3), 1.19 (s, 3H, CH_3 19), 1.22 (s, 3H, CH_3 17), 1.35 (s, 3H, CH_3 16), 1.84 (dd, J = 13.7, 4.1 Hz, 1H, H9α), 1.88 (m, 2H, H9β, OH7), 1.92 (m, 1H, H6β), 2.05 (d, J = 1.4 Hz, 3H, CH_3 18), 2.10 (m, 1H, H6α), 2.36 (dddd, J =1.4, 4.1, 9.9, 14.4 Hz, 1H, H5α), 2.47 (dd, J = 8.9, 15.4 Hz, 1H, H14β), 2.51 (m, 1H, H5β), 2.54 (dd, J = 4.8, 15.4 Hz, 1H, H14β), 2.86 (d, J = 5.5 Hz, 1H, H3), 3.59 (ddd, J = 4.5, 6.2, 11.3 Hz,

1H, H7), 4.38 (dd, J = 4.1, 9.1 Hz, 1H, H10), 4.56 (d, J = 5.5 Hz, 1H, H2), 4.69 (ddd, J =1.4, 4.8, 9.3 Hz 1H, H13). Anal. Calcd. for $C_{32}H_{56}O_7Si_2x.5H_2O$: C, 62.19; H, 9.30. Found C, 62.16; H, 9.22.

To a stirred solution of hydroxy ketone **18** (P_7=H) (179 mg, 0.29 mmol) in CH_2Cl_2 (9.5 mL), diisopropylethylamine (1.49 mL, 8.6 mmol) and tetrabutylammonium iodide (253 mg, 0.69 mmol) under nitrogen was added dropwise benzyloxymethylchloride (0.42 mL, 2.86 mmol). The reaction mixture was brought to reflux for 32 h, cooled to room temperature, poured into 100 mL of a saturated aqueous $NaHCO_3$ solution and extracted with two 100 mL portions of 50% ethyl acetate in hexanes. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield 249 mg of the hydroxy ketone as a yellowish oil. This material was purified by silica gel chromatography to yield 196 mg (92%) of ketone **18** (P_7=BOM, P_{10} = TES, P_{13} = TBS) as a colorless oil.

18 (P_7=BOM, P_{10} = TES, P_{13} = TBS): ^1H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 3H, TBS CH_3), 0.13 (s, 3H, TBS CH_3), 0.59 (q, J = 7.7 Hz, 6H, TES CH_2), 0.94 (s, 9H, TBS t-Bu), 0.94 (t, J = 7.7 Hz, 9H, TES CH_3), 1.22 (s, 3H, CH_3 17), 1.31 (s, 3H, CH_3 19), 1.33 (s, 3H, CH_3 16), 1.87 (dd, J = 12.1, 3.8 Hz, 1H, H9α), 1.98 (d, J = 1.4 Hz, 3H, CH_3 18), 1.99 (m, 2H, H6β, H9β), 2.21 (m, 1H, H6α), 2.34 (dd, J = 10.4, 12.1 Hz, 1H, H5α), 2.43 (dd, J = 9.3, 15.4 Hz, 1H, H14α), 2.55 (ddd, J = 5.5, 11.0, 13.7 Hz, 1H, H5β), 2.62 (dd, J = 5.0, 15.4 Hz, 1H, H14β), 2.74 (d, J = 5.0 Hz, 1H, H3), 3.38 (dd, J = 6.6, 11 Hz, 1H, H7), 4.38 (dd, J = 3.8, 10.4 Hz, 1H, H10), 4.56 (d, J = 5.0 Hz, 1H, H2), 4.58 (d, J =11.5 Hz 1H, $C\underline{H}_2Ph$), 4.64 (d, J =11.5 Hz 1H, $C\underline{H}_2Ph$), 4.68 (m, 2H, H13, OCH_2O), 4.82 (d, J =7.2 Hz 1H, OCH_2O), 7.31 (m, 5H, Ph).

Ketone **22a** (P_5=TMS). To a vigorously stirred solution of ketone **18** (P_7=BOM, P_{10} = TES, P_{13} = TBS) (315 mg, 0.42 mmol) in THF (10.5 mL), triethylamine (0.88 mL, 6.3 mmol) and trimethylsilyl chloride (0.53 mL, 4.2 mmol) under nitrogen at -78 °C was added dropwise down the side of the flask 1.35 mL of a 0.5 M solution (0.68 mmol) of LDA in THF. After 25 min, 2 mL of a saturated aqueous $NaHCO_3$ solution was added. The reaction mixture was diluted with 150 mL of hexanes and washed with 20 mL of a saturated aqueous $NaHCO_3$ solution and brine,

dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting oil was filtered through celite with hexanes and the filtrate was concentrated under reduced pressure to give 338 mg (99%) of the TMS enol ether **21a** (P_7=BOM, P_{10} = TES, P_{13} = TBS, P_4 = TMS) as a colorless oil. To a vigorously stirred solution of TMS enol ether **21a** (P_7=BOM, P_{10} = TES, P_{13} = TBS, P_4 = TMS) (224 mg, 0.274 mmol) in hexanes (2.8 mL) under nitrogen at room temperature was added dropwise 14.9 mL of a 0.02 M solution (0.30 mmol) of MCPBA in hexanes. After 5 h, 2 mL of a saturated aqueous $NaHCO_3$ solution and 2 mL of a 10% aqueous $Na_2S_2O_3$ solution were added. The reaction mixture was diluted with 150 mL of ethyl acetate and washed with 20 mL of a saturated aqueous $NaHCO_3$ solution, 20 mL of a 10% aqueous $Na_2S_2O_3$ solution, 20 mL of a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 231 mg of the crude material as a colorless oil. This material was used without further purification, or, alternatively, was purified by flash chromatography on silica gel to give 168 mg (74%) of **22a** (P_7=BOM, P_{10} = TES, P_{13} = TBS, P_5 = TMS) along with a mixture (15%) of **21a** and **18** which could be recycled.

22a (P_7=BOM, P_{10} = TES, P_{13} = TBS, P_5 = TMS): mp 50.5-52 °C, ^1H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 3H, TBS CH_3), 0.13 (s, 9H, TMS CH_3), 0.14 (s, 3H, TBS CH_3), 0.59 (q, J = 8.2 Hz, 6H, TES CH_2), 0.94 (s, 9H, TBS t-Bu), 0.94 (t, J = 8.2 Hz, 9H, TES CH_3), 1.24 (s, 3H, CH_3 17), 1.32 (s, 3H, CH_3 19), 1.33 (s, 3H, CH_3 16), 1.82 (dd, J = 11.3, 13.7 Hz, 1H, H9α), 1.95 (d, J = 1.4 Hz, 3H, CH_3 18), 1.98 (dd, J = 3.4, 13.7 Hz, 1H, H9β), 2.16 (ddd, J = 6.2, 7.2, 13.3 Hz, 1H, H6α), 2.40 (dt, J =11.4, 13.3 Hz, 6β), 2.43 (dd, J =9.2, 15.2 Hz, 1H, H14β), 2.63 (dd, J = 5.5, 15.2 Hz, 1H, H14α), 2.74 (d, J = 5.5 Hz, 1H, H3α), 3.40 (dd, J =7.2, 10.6 Hz, 1H, H7α),4.36 (dd, J = 3.4, 11.3 Hz, 1H, H10β), 4.40 (dd, J = 6.2, 12.0 Hz, 1H, H5α), 4.54 (d, J = 5,5 Hz, 1H, H2β), 4.57 (d, J =11.7 Hz 1H, C<u>H</u>$_2$Ph), 4.64 (d, J =11.7 Hz 1H, C<u>H</u>$_2$Ph), 4.68 (d, J =7.0 Hz 1H, OCH_2O), 4.74 (m, 1H, H13), 4.78 (d, J =7.0 Hz, 1H, OCH_2O), 7.31 (m, 5H, Ph). Anal. Calcd. for $C_{43}H_{72}O_9Si_3$: C, 63.19; H, 8.88. Found C, 63.19; H, 8.92.

Ketone **22a** (P_5 = H). To a vigorously stirred solution of crude **22a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, P_5 = TMS) (231 mg, 0.274 mmol) in acetonitrile (7 mL) at 0°C was added dropwise 7 mL

of a 1:10:10 (by volume) mixture of 48% aqueous HF:pyridine:acetonitrile . After stirring for 20 min, 2 mL of a saturated aqueous $NaHCO_3$ solution was added. The reaction mixture was diluted with 150 mL of ethyl acetate and washed with 30 mL of a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 223 mg of the crude alcohol as a colorless oil. This material was purified by silica gel chromatography to yield 155 mg (74%) of ketone **22a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, P_5 = H), 15 mg (7%) of the 5β-hydroxy ketone and 33 mg (14% recoverable material) of a 1:1 mixture of TMS enol ether **21a** and ketone **18**.

22a (P_7 = BOM, P_{10} = TES, P_{13} = TBS, P_5 = H): ^1H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 3H, TBS CH_3), 0.14 (s, 3H, TBS CH_3), 0.59 (q, J = 8.2 Hz, 6H, TES CH_2), 0.94 (s, 9H, TBS t-Bu), 0.94 (t, J = 8.2 Hz, 9H, TES CH_3), 1.23 (s, 3H, CH_3 19), 1.32 (s, 3H, CH_3 17), 1.33 (s, 3H, CH_3 16), 1.83 (dd, J = 11.0, 13.7 Hz, 1H, H6β), 1.97 (d, J = 1.4 Hz, 3H, H18), 2.01 (dd, J = 3.2, 13.7 Hz, 1H, H9β), 2.11 (ddd, J = 5.5, 7.7, 13.7 Hz, 1H, H6α), 2.47 (dd, J = 8.7, 15.4 Hz, 1H, H14β), 2.57 (m, 2H, H14α, H9α), 2.88 (d, J = 5.5 Hz, 1H, H3α), 3.39 (dd, J = 7.7, 11.0 Hz, 1H, H7α), 3.41 (d, J = 3.3 Hz, 1H, OH-5), 4.38 (m, 2H, H5β, H10), 4.55 (d, J = 5.5 Hz, 1H, H2β), 4.57 (d, J =11.5 Hz 1H, CH_2Ph), 4.62 (d, J =11.5 Hz 1H, CH_2Ph), 4.72 (m, 2H, H13β, OCH_2O), 4.80 (d, J =7.1 Hz 1H, OCH_2O), 7.31 (m, 5H, Ph).

Ketone **22a** (P_5=TMS) from ketone **22a** (P_5=H). To a vigorously stirred solution of 5-hydroxy-4-ketone **22a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, P_5 = H) (51 mg, 0.067 mmol) in CH_2Cl_2 (2.2 mL) and triethylamine (0.14 mL, 1.0 mmol) under nitrogen at 0 °C was added trimethylsilylchloride (0.041 mL, 0.34 mmol). After 0.5 h, the reaction mixture was quenched with 5 mL of a saturated aqueous $NaHCO_3$ solution and extracted with 150 mL hexanes. The organic phase was washed with 50 mL of a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 56 mg a colorless oil. This material was filtered through silica gel and the filtrate was concentrated under reduced pressure to yield 54 mg (96 %) of ketone **22a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, P_5 = TMS).

Alcohol **23a**. To a stirred solution of ketone **22a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, P_5 = TMS)

(18.9 mg, 0.023 mmol) in CH_2Cl_2 (4 mL) under nitrogen at -65 °C was added dropwise a 0.073 mL of a 3.1 M solution of MeMgBr in ether (0.23 mmol). The reaction mixture was allowed to warm to -48 °C, stirred for 16.5 h and then quenched with 0.13 mL of a 2.0M solution of AcOH in THF (0.25 mmol) and then poured into a stirring mixture of 50 mL of a saturated aqueous $NaHCO_3$ solution and 50 mL of ethyl acetate. The aqueous phase was extracted with 50 mL ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield 20.5 mg of a colorless oil. This material was purified by silica gel chromatography to yield 18.4 mg (95%) of alcohol **23a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, P_5 = TMS) as a colorless oil.

23a (P_7 = BOM, P_{10} = TES, P_{13} = TBS, P_5 = TMS): [1]H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 9H, TMS), 0.11 (s, 3H, TBS CH_3), 0.12 (s, 3H, TBS CH_3), 0.56 (q, J = 7.9 Hz, 6H, TES CH_2), 0.92 (t, J = 7.9 Hz, 9H, TES CH_3), 0.93 (s, 9H, TBS t-Bu), 1.25 (s, 3H, CH_3 17), 1.28 (s, 3H, CH_3 19), 1.33 (s, 3H, CH_3 20), 1.34 (s, 3H, CH_3 16), 1.74 (ddd, J = 3.8, 4.1, 13.0 Hz, 1H, H6α), 1.99 (d, J = 1.4 Hz, 3H, H18), 2.01 (dd, J = 11.3, 13.0 Hz, 1H, H9α), 2.06 (m, 2H, H3, H9β), 2.13 (ddd, J = 1.7, 12.3, 13.0 Hz, 1H, H6β), 2.37 (dd, J = 5.5, 15.0 Hz, 1H, H14α), 2.54 (dd, J = 9.2, 15.0 Hz, 1H, H14β), 2.96 (s, 1H, OH-4), 3.51 (dd, J = 1.7, 4.1 Hz, 1H, H5), 3.73 (dd, J = 3.8, 12.3 Hz, 1H, H7α), 4.32 (dd, J = 4.1, 11.3 Hz, 1H, H10β), 4.64 (s, 2H, $C\underline{H}_2Ph$), 4.72 (d, J = 6.8 Hz, 1H, OCH_2O), 4.80 (m, 3H, H2, H13, OCH_2O), 7.31 (m, 5H, Ph). Anal. Calcd. for $C_{44}H_{76}O_9Si_3$: C, 63.42; H, 9.19. Found C, 63.40; H, 9.15.

Hydroxy olefin **24a**. To a refluxing solution of alcohol **23a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, P_5 = TMS) (46.7 mg, 0.055 mmol) in toluene (1.1 mL) was added 1.1 mL of a 0.1M solution of Burgess reagent in toluene (0.11 mmol). The mixture was refluxed for 20 min then cooled to room temperature, diluted with ethyl acetate, washed with a saturated solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and filtered. Concentration of the filtrate under vacuum yielded 46 mg of crude olefin. This material was used without further purification.

To a stirred solution of this crude olefin (46 mg, 0.055 mmol) in acetonitrile (2.5 mL) at 0 °C was added 2.5 mL of a 1:10:10 (by volume) mixture of 48% aqueous HF : pyridine : acetonitrile. The

mixture was stirred at 0 °C for 20 min, quenched with a saturated solution of $NaHCO_3$ and extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and filtered. Concentration of the filtrate under vacuum yielded 48 mg of a colorless oil which was purified by silica gel chromatography to yield 25.9 mg (62%) of hydroxy olefin **24a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, R = H) as well as 2.1 mg of unreacted alcohol **23a** (4%).

24a (P_7 = BOM, P_{10} = TES, P_{13} = TBS, R = H): mp 66-68 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 3H, TBS CH_3), 0.13 (s, 3H, TBS CH_3), 0.59 (q, J = 7.9 Hz, 6H, TES CH_2), 0.94 (t, J = 7.9 Hz, 9H, TES CH_3), 0.95 (s, 9H, TBS t-Bu), 1.18 (s, 3H, CH_3 19), 1.23 (s, 3H, CH_3 17), 1.35 (s, 3H, CH_3 16), 1.73 (d, 1H, J = 3.4 Hz, OH5), 1.83 (dd, J = 9.9, 10.5 Hz, 1H, H9α), 1.91 (ddd, J = 7.2, 7.5, 13.4 Hz, 1H, H6α), 1.97 (dd, J = 3.8, 9.9 Hz, 1H, H9β), 2.03 (d, J = 1.4 Hz, 3H, 18), 2.14 (ddd, J = 9.6, 9.6, 13.4 Hz, 1H, H6β) 2.35 (dd, J = 5.1, 15.4 Hz, 1H, H14α), 2.50 (dd, J =9.6, 15.4 Hz, 1H, H14β), 3.03 (d, J = 5.8 Hz, 1H, H3α), 3.44 (dd, J = 7.5, 9.6, Hz, 1H, H7α), 4.38 (m, 2H, H10, H5), 4.54 (d, J = 5.8 Hz, 1H, H2), 4.58 (d, J =11.6 Hz, 1H, C<u>H</u>$_2$Ph), 4.62 (d, J =11.6 Hz, 1H, C<u>H</u>$_2$Ph), 4.73 (d, J =7.0 Hz, 1H, OCH_2O), 4.75 (m, 1H, H13), 4.79 (d, J =7.0 Hz, 1H, OCH_2O), 5.00 (s, 1H, H20*E*), 5.18 (s, 1H, H20*Z*), 7.31 (m, 5H, Ph). Anal. Calcd. for $C_{41}H_{66}O_8Si_2$x$0.5H_2O$: C, 65.47; H, 8.98. Found C, 65.63; H, 8.97.

Allyl mesylate **24aa**. To a stirred solution of allyl alcohol **24a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, R = H) (11.5 mg, 0.0154 mmol) in pyridine (0.6 mL) under nitrogen at 0 °C was added dropwise methanesulfonyl chloride (0.02 mL, 0.258 mmol). After 45 min, a saturated aqueous $NaHCO_3$ solution (0.05 mL) was added. The mixture was stirred for 10 min, poured into 20 mL of a saturated aqueous $NaHCO_3$ solution and extracted with 40% ethyl acetate/hexane (20 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 13 mg of **24aa** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, R = Ms) as a colorless oil. This material was used without further purification.

24aa (P_7 = BOM, P_{10} = TES, P_{13} = TBS, R = Ms): ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.12 (s, 3H, TBS CH_3), δ 0.13 (s, 3H, TBS CH_3), 0.58 (q, J = 7.9 Hz, 6H, TES CH_2), 0.93 (s, 9H,

TBS t-Bu), 0.94 (t, J = 7.9 Hz, 9H, TES CH_3), 1.23 (s, 3H, CH_3 17), 1.22 (s, 3H, CH_3 19), 1.34 (s, 3H, CH_3 16), 1.80 (br t, J =13 Hz, 1H, H9α), 1.98 (m, 1H, H6), 1.79 (ddd, J = 2.2, 5.5, 15.1 Hz, 1H, H14α), 2.01 (d, J = 1.1 Hz, 1H, $CH_3$18), 2.06 (dd, J = 3.3, 13.7 Hz, 1H, H9β), 2.01 (br s, 3H, CH3 18), 2.22-2.32 (m, 3H, H14α, H6α, H6β), 2.54 (dd, J = 9.9, 15.4 Hz, 1H, H14β), 3.02 (s, 3H, OSO_2CH_3), 3.05 (d, J = 6.0 Hz, 1H, H3α), 3.45 (t, J = 8.5 Hz, 1H, H7α), 4.37 (dd, J =3.6, 11.0 Hz, 1H, H10β), 4.57 (d, J = 6.0 Hz, 1H, H2β), 4.59 (q, 2H, $PhC\underline{H}_2O$), 4.69 (d, J = 7.1 Hz, 1H, OCH_2O), 4.74 (m, 1H, H13β), 4.76 (d, J = 7.1 Hz, 1H, OCH_2O), 5.03 (br t, J = 8.5 Hz, 1H, H5β), 5.09 (br s, 1H, H20), 5.24 (br s, 1H, H20), 7.35 (m, 5H, Ph).

Triol **25a**. To a stirred solution of allyl alcohol **24a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, R = H) (45 mg, 0.0606 mmol) in a mixture of pyridine (0.32 mL) and ether (3.2 mL) under nitrogen at 0 °C was added a 0.157 M solution of OsO_4 in THF (0.42 mL, 0.066 mmole). After 12 h at 0 °C, $NaHSO_3$ (530 mg), pyridine (0.3 mL), THF (2 mL) and water (3 mL) were added. The mixture was vigorously stirred at room temperature for 14 h, poured into 50 mL of a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (40 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 60 mg of a pale yellow oil, which was column chromatographed (30% ethyl acetate/hexane) to yield 34.3 mg (73 %) of triol **25a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS).

25a (P_7 = BOM, P_{10} = TES, P_{13} = TBS): ^{1}H NMR (500 MHz, $CDCl_3$); δ 0.11 (s, 6H, TBS CH_3), 0.60 (ddd, J = 9.0 Hz, 6H, TES CH_2), 0.79 (s, 3H, CH_3 19), 0.93 (s, 9H, TBS t-Bu), 0.94 (dd, J = 9.0 Hz, 9H, TES CH_3), 1.22 (s, 3H, CH_3 17), 1.35 (s, 3H, CH_3 16), 1.64 (dd, J = 5.6, 16.4 Hz, 1H, H9β), 1.70 (m, 1H, H6β), 2.22 (dd, J = 2.7, 16.8 Hz, 1H, H9α), 2.23 (d, J = 0.7 Hz, 3H, CH_3 18),, 2.36 (dd, J = 9.2, 15.0 Hz, 1H, H14β), 2.45 (m, 1H, H6α), 2.96 (s, 1H, OH5), 3.21 (dd, 6.9, 15.0 Hz, 1H, H14α), 3.42 (d, J = 5.0 Hz, 1H, H3α), 3.53 (m, 1H, H20), 3.38 (s, 1H, OH4), 3.70 (t, J = 3.0 Hz, 1H, H5β), 4.04 (br d, J = 11 Hz, 1H, H20), 4.06 (dd, J = 11.5, 5.0 Hz, 1H, H7α), 4.48 (d, J = 5.0 Hz, 1H, H2β), 4.49 (d, J = 12.0 Hz, 1H, $PhC\underline{H}_2O$), 4.53 (br s, 1H, H10β), 4.71 (m, 1H, H13β), 4.72 (d, J = 12.0 Hz, 1H, $PhC\underline{H}_2O$), 4.85 (d, J = 6.8 Hz, 1H, OCH_2O), 4.98 (d, J = 6.8 Hz, 1H, OCH_2O), 7.34 (m, 5H,

Ph). Anal. Calcd. for $C_{41}H_{68}O_{10}Si_2$: C, 63.36; H, 8.82. Found C, 63.19; H, 8.75.

Diol mesylate **26a.** To a stirred solution of allyl mesylate 24aa (P_7 = BOM, P_{10} = TES, P_{13} = TBS, R = Ms) (5 mg, 0.0064 mmol) in a mixture of pyridine (0.4 mL) and THF (0.4 mL) under nitrogen at room temperature was added a 0.157 M solution of OsO_4 in THF (0.06 mL). After 7 h, $NaHSO_3$ (150 mg) and water (0.2 mL) were added. The mixture was vigorously stirred for 14 h, poured into 20 mL of a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (20 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 6 mg of a pale yellow oil. The oil was column chromatographed (40% ethyl acetate/hexane) to yield 2.7 mg (50%) of diol mesylate 26a (P_7 = BOM, P_{10} = TES, P_{13} = TBS, R = Ms).

26a (P_7 = BOM, P_{10} = TES, P_{13} = TBS, R = Ms): ^{1}H NMR (500 MHz, $CDCl_3$); δ 0.14 (s, 6H, TBS CH_3), 0.58 (ddd, J = 8.0 Hz, 6H, TES CH_2), 0.89 (s, 3H, CH_3 19), 0.93 (s, 9H, TBS t-Bu), 0.94 (dd, J = 8.0 Hz, 9H, TES CH_3), 1.31 (s, 3H, CH_3 17), 1.37 (s, 3H, CH_3 16), 1.76 (dd, J = 5.5, 15.1, 1Hz, H9β), 1.95 (m, 1H, H6β), 2.23 (d, J = 0.7 Hz, 3H, CH_3 18), 2.25 (dd, J = 4.8, 15.1 Hz, 1H, H9α), 2.39 (dd, J = 9.2, 15.1 Hz, 1H, H14β), 2.45 (m, 1H, H6α), 2.89 (dd, 6.8, 15.1 Hz, 1H, H14α), 3.05 (d, J = 3.4 Hz, 1H, H3α), 3.06 (s, 3H, OSO_2CH_3), 3.35 (s, 1H, OH4), 3.52 (m, 1H, H20), 3.92 (dd, J = 4.5, 11.6 Hz, 1H, H7α), 4.13 (dd, J = 1.0, 11.3 Hz, 1H, H20), 4.46 (br d, J = 4.5 Hz, 1H, H10), 4.52 (d, J = 3.4 Hz, 1H, H2), 4.54 (d, J = 12.0 Hz, 1H, PhC$\underline{H}_2$O), 4.70 (d, J = 12.0 Hz, 1H, PhC$\underline{H}_2$O), 4.83 (d, J = 6.9 Hz, 1H, OCH_2O), 4.84 (m, 1H, H5β), 4.92 (m, 1H, H13β), 4.93 (d, J = 6.9 Hz, 1H, OCH_2O), 7.34 (m, 5H, Ph).

Diol tosylate **26aa.** To a stirred solution of triol 25a (P_7 = BOM, P_{10} = TES, P_{13} = TBS) (37 mg, 0.0476 mmole) in CH_2Cl_2 (0.4 mL) under nitrogen at -78 °C was added triethylamine (0.25 mL) followed by trimethylchlorosilane (0.075 mL). The solution was stirred at -78 °C for 1 h, poured into 20 mL of a saturated aqueous $NaHCO_3$ solution and extracted with chloroform (30 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 38.2 mg of a colorless oil. This oil was dissolved in THF (0.5 mL) and

cooled to -78 °C. To this solution was added a 0.2 M solution of LDA in THF (0.9 mL, 0.18 mmole). After 20 min at -78°C, p-toluenesulfonyl chloride (35 mg, 0.183 mmole) was added. After stirring at -35 °C for 3 h, MeOH (0.2 mL) and diethylamine (0.3 mL) were added. The solution was stirred at -35 °C for 30 min and poured into 30 mL of a saturated aqueous $NaHCO_3$ solution and extracted with chloroform (40 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 58 mg of a colorless oil. The oil was dissolved in acetonitrile (3.6 mL) and pyridine (3.6 mL). To this solution at 0 °C was added 48 % aqueous solution of HF (0.36 mL). The solution was stirred at 0 °C for 15 min, poured into 30 mL of a saturated aqueous $NaHCO_3$ solution and extracted with chloroform (40 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 56 mg of crude diol tosylate **26aa**. Column chromatography (40% ethylacetate/hexane) yielded 34 mg (80 %) diol tosylate **26aa** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, R = Ts).

26aa (P_7 = BOM, P_{10} = TES, P_{13} = TBS, R = Ts). ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.18 (s, 6H, TBS CH_3), 0.58 (d, J = 12.5 Hz, 6H, TES CH_2), 0.82 (s, 3H, CH_3 19), 0.94 (dd, J=13.0 Hz, 9H, TES CH_3), 0.97 (s, 9H, TBS t-Bu), 1.28 (s, 3H, CH_3 17), 1.34 (s, 3H, CH_3 16), 1.67 (dd, J = 16.5, 4.4 Hz, 1H, H9β), 1.80 (m, 1H, H6β), 2.13 (dd, J = 16.5, 4.4 Hz, 1H, H9α), 2.18 (m, 1H, H6α), 2.24 (s, 3H, CH_3 18), 2.33 (s, 3H, CH_3Ph), 2.42 (dd, J = 14.8, 9.3 Hz, 1H, H14β), 2.90 (m, 1H, H14α), 2.93 (br s, 1H, OH4), 3.08 (br d, J = 3.3 Hz, 1H, H3α), 3.38 (br t, J = 11.0 Hz, 1H, H7α), 3.87 (m, 1H, H20), 4.09 (br d, J = 9.9 Hz, 1H, H20), 4.52 (d, J = 3.3 Hz, 1H, H2β), 4.45 (br d, J = 4.4 Hz, 1H, H10β), 4.46 (d, J = 12.1 Hz, 1H, PhCH_2O), 4.59 (d, J = 12.1 Hz, 1H, PhC$\underline{H}_2$O), 4.66 (br t, J = 3.8 Hz, 1H, H5β), 4.75 (d, J = 7.1 Hz, 1H, OCH_2O), 4.83 (d, J = 7.1 Hz, 1H, OCH_2O), 4.89 (br dd, J = 7.7, 6.6 Hz, 1H, H13β), 7.14 (d, J = 8.2 Hz, 2H, SO_2Ph), 7.34 (m, 5H, OCH_2Ph), 7.75 (d, J = 8.2 Hz, 2H, SO_2Ph).

Oxetane **27a** from diol mesylate **26a**. To a stirred solution of diol mesylate **26a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, R = Ms) (2.7 mg) in toluene (0.4 mL) under nitrogen at room temperature was added diisopropyl ethylamine (0.008 mL). The solution was refluxed for 3.5 h, cooled to room

temperature, poured into 20 mL of a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (20 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 3 mg of a pale yellow oil. The oil was column chromatographed (30% ethyl acetate/hexane) to yield 1 mg (42%) of oxetane **27a**.

27a (P_7 = BOM, P_{10} = TES, P_{13} = TBS): ^{1}H NMR (500 MHz, $CDCl_3$); δ 0.10 (s, 6H, TBS CH_3), 0.59 (dd, J = 8.0 Hz, 6H, TES CH_2), 0.92 (s, 9H, TBS t-Bu), 0.94 (dd, J = 8.0 Hz, 9H, TES CH_3), 1.20 (s, 3H, CH_3 17), 1.26 (s, 3H, CH_3 19), 1.32 (s, 3H, CH_3 16), 1.93 (dd, J = 11.3, 13.4 Hz, 1H, H9α), 1.98 (d, J = 1.4 Hz, 3H, CH_3 18), 2.06 (dd, J = 6.0, 18.6 Hz, 1H, H6β), 2.11 (dd, J = 4.5, 13.4 Hz, 1H, H9β), 2.14 (d, J = 5.5 Hz, 1H, H3α), 2.41 (dd, J = 9.2, 15.1 Hz, 1H, H14β), 2.43 (m, 1H, H6α), 2.54 (s, 1H, OH4), 2.76 (dd, J = 5.2, 15.1 Hz, H14α), 3.21 (dd, J = 3.4, 13.0 Hz, 1H, H7α), 4.36 (d, J = 8.6 Hz, 1H, H20α), 4.37 (dd, J = 4.1, 11.3 Hz, 1H, H10β), 4.40 (br d, J = 8.2 Hz, 1H, H5α), 4.60 (d, J = 5.5 Hz, 1H, H2β), 4.61 (d, J = 12.6 Hz, 1H, PhC$\underline{H}_2$O), 4.67 (m, 1H, H13β), 4.69 (d, J = 12.6 Hz, 1H, PhC$\underline{H}_2$O), 4.75 (d, J = 7.5 Hz, 1H, OCH_2O), 4.86 (d, J = 7.5 Hz, 1H, OCH_2O), 4.91 (dd, J = 0.7, 8.6 Hz, 1H, H20β), 7.34 (m, 5H, Ph). Anal. Calcd. for $C_{41}H_{66}O_9Si_2$: C, 64.87; H, 8.76. Found C, 64.61; H, 8.78.

Oxetane **27a** from diol tosylate **26aa**. To a stirred solution of diol tosylate **26aa** (P_7 = BOM, P_{10} = TES, P_{13} = TBS, R = Ts) (33 mg, 0.0354 mmole) in toluene (3.3 mL) under nitrogen at room temperature was added DBU (0.11 mL, 0.73 mmole). The solution was heated at 80 °C for 10 min, then the temperature was increased up to 110 °C during a 40 min period, maintained at 110 °C for 30 more min and cooled to room temperature.The solution was filtered through a short pad of silica gel using 30% ethyl acetate/hexane as eluent. The filtrate was concentrated to give 25 mg of crude **27a**, which was column chromatographed (30% ethyl acetate/hexane) to yield 21 mg (78 %) of oxetane **27a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS).

Oxetane **29**. To a stirred solution of oxetane **27a** (P_7 = BOM, P_{10} = TES, P_{13} = TBS) (21 mg, 0.0276 mmloe) and dimethylaminopyridine (3.4 mg, 0.0278 mmole) in pyridine (110 µL, 1.37 mmole) under nitrogen at room temperature was added acetic anhydride (26 µL, 0.276 mmole).

The solution was stirred for 25h, diluted with ethyl acetate, poured into 20 mL of saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (20 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 26 mg of a pale yellow oil, which was column chromatographed (25% ethyl acetate/hexane) to yield 16 mg (72%) of oxetane 29 (P_7 = BOM, P_{10} = TES, P_{13} = TBS).

29 (P_7 = BOM, P_{10} = TES, P_{13} = TBS): ^{1}H NMR (500 MHz, $CDCl_3$); δ 0.10 (s, 3H, TBS CH_3), 0.12 (s, 3H, TBS CH_3), 0.56 (q, 6H, TES CH_2), 0.92 (t, 9H, TES CH_3), 0.94 (s, 9H, TBS t-Bu), 1.35 (s, 3H, CH_3 16), 1.30 (s, 3H, CH_3 17), 1.29 (s, 3H, CH_3 19), 1.96 (br t, J = 13.0 Hz, 1H, H9α), 1.98 (d, J = 1.4 Hz, 3H, CH_3 18), 2.02 (dd, J = 7.5, 13.0, 1H, H9β), 2.07 (dt, J = 8.0, 13.0 Hz, 1H, H6β), 2.13(s, 3H, OAc), 2.24 (dd, J = 3.4, 15.0 Hz, 1H, H14α), 2.40 (dd, J = 8.6, 15.0 Hz, 1H, H14β), 2.51 (ddd, J = 4.1, 9.2, 15.0 Hz, 1H, H6α), 2.63 (d, J = 6.5 Hz, 1H, H3α), 3.69 (dd, J = 4.1, 13.0 Hz, H7α), 4.35 (dd, J = 3.4, 11.3 Hz, 1H, H10β), 4.64 (m, 4H, $PhC\underline{H}_2O$, H2β, H5α), 4.75 (d, J = 7.2 Hz, 1H, OCH_2O), 4.76 (br d, J = 9.2 Hz, 1H, H20), 4.83 (d, J = 7.2 Hz, 1H, OCH_2O), 4.85 (br d, J = 9.2 Hz, 1H, H20), 4.88 (br t, J = 8.2 Hz, 1H, H13β), 7.35 (m, 5H, Ph).

Benzoate 30. To a stirred solution of oxetane 29 (P_7 = BOM, P_{10} = TES, P_{13} = TBS) (6 mg, 0.0075 mmol) in THF (0.5 mL) under nitrogen at -78 °C was added a 0.3M solution of phenyllithium in ether (44 μL, 0.013 mmol). The solution was stirred at -78 °C for 15 min and quenched with a 10% solution of acetic acid in THF. The solution was diluted with ethyl acetate, poured into 20 mL of a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (20 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 8 mg of a pale yellow oil. The oil was column chromatographed (25% ethyl acetate/hexane) to yield 6.2 mg (94%) of benzoate 30 (P_7 = BOM, P_{13} = TBS, R = TES).

30 (P_7 = BOM, P_{13} = TBS, R = TES): ^{1}H NMR (500 MHz, $CDCl_3$); δ 0.09 (s, 3H, TBS CH_3), 0.14 (s, 3H, TBS CH_3), 0.60 (ddd, 6H, TES CH_2), 0.94 (s, 9H, TBS t-Bu), 0.96 (t, 6H, TES CH_3), 1.23 (s, 3H, CH_3 17), 1.38 (s, 3H, CH_3 19), 1.46 (s, 3H, CH_3 16), 1.69 (s, 1H, OH1), 1.97 (ddd, J = 14.5, 10.0, 3.1 Hz, 1H, H6β), 2.05 (dd, J = 16.1, 5.1 Hz, 1H, H9β), 2.09 (dd,

J = 15.1, 6.2 Hz, 1H, H14β), 2.13 (s, 3H, CH_3 18), 2.22 (dd, J = 15.1, 8.2 Hz, 1H, H14α), 2.23 (dd, J= 15.0, 8.5 Hz, 1H, H9β), 2.24 (s, 1H, OAc 4), 2.38 (dd, J = 16.1, 4.1 Hz, 1H, H9α), 2.67 (m, 1H, H6α), 3.40 (d, J = 6.2 Hz, 1H, H3α), 3.99 (dd, J = 10.1, 6.8 Hz, 1H, H7α), 4.20 (d, J= 8.2 Hz, 1H, H20β), 4.29 (d, J = 8.2 Hz, 1H, H20α), 4.49 (d,J= 12.0 Hz, 1H, PhC<u>H</u>$_2$O), 4.63 (br t, 1H, H10β), 4.74 (d,J= 12.0 Hz, 1H, PhC<u>H</u>$_2$O), 4.92 (d, J = 6.9 Hz, 1H, OCH_2O), 4.91-4.95 (m, 2H, H13β & H5α), 5.01(d, J = 6.9 Hz, 1H, OCH_2O), 5.66 (d, J = 6.2 Hz, 1H, H2β), 7.28 (m, 1H, <u>Ph</u>CH_2), 7.35 (m, 4H, <u>Ph</u>CH_2), 7.48 (m, 2H, PhCOO -*m*), 7.59 (m, 1H, PhCOO -*p*), 8.11 (m, 2H, PhCOO-*o*).

Alcohol 31. To a solution of benzoate 30 (P_7 = BOM, P_{13} = TBS, R = TES) (6.2 mg, 0.007 mmol) in 2 mL of THF was added 0.1 mL of a 0.1 M solution of TBAF in THF. The mixture was stirred for 2 h at 25 °C under nitrogen. The reaction mixture was diluted with 10 mL of ethyl acetate, then poured into 10 mL of a saturated aqueous $NaHCO_3$ solution. The organic phase was washed with 10 mL of a saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 4.5 mg (93%) of alcohol 31 (P_7 = BOM, P_{13} = TBS, R = H).

31 (P_7 = BOM, P_{13} = TBS, R = H): mp 213-216 °C ^{1}H NMR (500 MHz, $CDCl_3$); δ 0.10 (s, 3H, TBS CH_3), 0.15 (s, 3H, TBS CH_3), 0.94 (s, 9H, TBS t-Bu), 1.26 (s, 3H, CH_3 17), 1.39 (s, 3H, CH_3 19), 1.45 (s, 3H, CH_3 16), 1.68 (s, 1H, OH1), 1.89 (ddd, J = 14.5, 10.0, 2.5 Hz, 1H, H6β), 2.10 (dd, J = 15.0, 9.0 Hz, 1H, H14β), 2.15 (dd, J = 15.0, 8.0 Hz, 1H, H14α), 2.18 (s, 3H, CH_3 18), 2.23 (dd, J= 15.0, 8.5 Hz, 1H, H9β), 2.26 (s, 1H, OAc 4), 2.40 (dd, J = 15.0, 3.5 Hz, 1H, H9α), 2.68 (m, 1H, H6α), 2.90 (br s, 1H, OH10), 3.54 (d, J = 6.0 Hz, 1H, H3α), 4.16 (d, J= 8.0 Hz, 1H, H20β), 4.23 (dd, J = 10.0, 7.0 Hz, 1H, H7α), 4.30 (d, J = 8.0 Hz, 1H, H20α), 4.68 (dd,J= 15 Hz, 2H, PhC<u>H</u>$_2$O), 4.78 (m, 1H, H10β), 4.87 (d, J = 6.5 Hz, 1H, OCH_2O), 4.95 (t, J = 2.0 Hz, 1H, H20α), 4.92 (d, J = 7.0 Hz, 1H, OCH_2O), 4.93 (br d, J = 2.0 Hz, 1H, H13β), 4.96 (br d, J = 6.5 Hz, 1H, H5α), 4.97 (d, J = 6.5 Hz, 1H, OCH_2O), 5.68 (d, J = 6.0 Hz, 1H, H2β), 7.28 (m, 1H, <u>Ph</u>CH_2O), 7.35 (m, 4H, <u>Ph</u>CH_2O), 7.40 (m, 2H, PhCOO-*m*), 7.59 (m, 1H, PhCOO-*p*), 8.13 (m, 2H, PhCOO-*o*). Anal. Calcd. for $C_{43}H_{60}O_{10}Si$x$0.5H_2O$: C, 66.72; H, 7.94. Found C, 66.75; H, 7.96.

Alcohol 31 through Alcohol 30a. To a stirred solution of oxetane 29 (P_7 = BOM, P_{10} = TES, P_{13} = TBS) (16 mg, 0.02 mmole) in acetonitrile (0.33 mL) at 0 °C was added a 4% solution of HF-pyridine complex in acetonitrile (0.8 mL). The solution was stirred at 0 °C for 11 h, diluted with ethyl acetate, poured into 20 mL of a saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$ (30 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 13.5 mg (0.0196 mmole) of **30a** as an oil. This oil was dissolved in THF (1 mL) and cooled to -78 °C. To this solution at -78 °C was added a 0.285 M solution of phenyllithium in THF (0.144 mL, 2.1 eq.). After 10 min, the solution was poured into 20 mL of saturated aqueous $NaHCO_3$ solution and $CHCl_3$ (30 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 16 mg of a pale yellow oil, which was crystalized to yield 12.7 mg (85%) of benzoate **31** (P_7 = BOM, P_{13} = TBS, R = H).

Ketone 32. To a solution of benzoate **31** (P_7 = BOM, P_{13} = TBS, R = H) (18 mg, 0.235 mmole) and 4-methylmorpholine N-oxide (18 mg, 0.154 mmole) in CH_2Cl_2 (2.6 mL) at room temperature was added tetrapropylammonium perruthenate (6 mg, 0.017 mmole). The solution was stirred at room temperature for 15 min and filtered through silica gel with 30 % ethyl acetate/hexane. The filtrate was concentrated under reduced pressure to yield ketobenzoate 32 (P_7 = BOM, P_{13} = TBS) (18 mg, 100%).

32 (P_7 = MOP, P_{13} = TBS): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 3H, TBS CH_3), 0.16 (s, 3H, TBS CH_3), 0.94 (s, 9H, TBS t-Bu), 1.25 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.44 (s, 6H, MOP CH_3), 1.49 (s, 3H, CH_3), 1.75 (s, 1H, OH1), 1.76 (m, 1H, H6), 1.83 (s, 3H, CH_3 18), 2.21 (dd, J = 7, 15 Hz, 1H, H14), 2.25 (s, 3H, OAc), 2.29 (dd, J = 8, 15 Hz, 1H, H14), 2.61 (d, J = 16 Hz, 1H, H9), 2.74 (ddd, J = 8, 9, 17 Hz, 1H, H6), 3.19 (s, 3H, MOP OCH_3), 3.20 (d, J = 6 Hz, 1H, H3α), 3.32 (d, J = 16 Hz, 1H, H9), 3.78 (dd, J = 8, 10 Hz, 1H, H7), 4.15 (d, J = 8 Hz, 1H, H20), 4.34 (d, J = 8 Hz, 1H, H20), 4.89 (d, J = 9 Hz, 1H, H5), 5.04 (m, 1H, H13), 5.90 (d, J = 6 Hz, 1H, H2), 7.50 (m, 2H, PhCOO -*m*), 7.62 (m, 1H, PhCOO -*p*), 8.24 (m, 2H, PhCOO -*o*).

32 (P_7 = TES, P_{13} = TBS): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 3H, TBS CH_3), 0.16 (s,

3H, TBS CH_3), 0.65 (q, J = 8 Hz, 3H, TES CH_3), 0.66 (q, J = 8 Hz, 3H, TES CH_3), 0.94 (s, 9H, TBS t-Bu), 1.00 (t, J = 8 Hz, 3H, TES CH_2), 1.24(s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.75 (s, 1H, OH1), 1.80 (m, 1H, H6), 1.81 (s, 3H, CH_3 18), 2.20 (dd, J = 9, 15 Hz, 1H, H14), 2.26 (s, 3H, OAc CH_3), 2.29 (dd, J = 8, 15 Hz, 1H, H14), 2.48 (ddd, J = 8, 9, 17 Hz, 1H, H6), 2.58 (d, J = 17 Hz, 1H, H9), 3.15 (d, J = 6 Hz, 1H, H3α), 3.36 (d, J = 17 Hz, 1H, H9), 3.79 (dd, J = 7, 9 Hz, 1H, H7), 4.14 (d, J = 8 Hz, 1H, H20), 4.33 (d, J = 8 Hz, 1H, H20), 4.90 (d, J = 9 Hz, 1H, H5), 5.04 (m, 1H, H13), 5.90 (d, J = 6 Hz, 1H, H2), 7.49 (m, 2H, PhCOO -*m*), 7.61 (m, 1H, PhCOO -*p*), 8.13 (m, 2H, PhCOO -*o*).

32 (P_7 = BOM, P_{13} = TBS): ^{1}H NMR (500 MHz, $CDCl_3$); δ 0.16 (s, 3H, TBS CH_3), 0.18 (s, 3H, TBS CH_3), 0.94 (s, 9H, TBS t-Bu), 1.26 (s, 3H, CH_3 17), 1.47 (s, 3H, CH_3 19), 1.52 (s, 3H, CH_3 16), 1.76 (s, 1H, OH1), 1.83 (d, 3H,J = 0.5 Hz, CH_3 18), 1.89 (ddd, J = 15.0, 9.5, 1.5 Hz, 1H, H6β), 2.21 (dd, J = 15.0, 9.0 Hz, 1H, H14β), 2.26 (s, 1H, OAc 4), 2.29 (dd, J = 15.0, 8.0 Hz, 1H, H14α), 2.72 (m, 1H, H6α), 2.75 (d, J = 16 Hz, 1H, H9α), 3.18 (d, J = 6.5 Hz, 1H, H3α), 3.26 (d, J = 16.5 Hz, H9α), 3.65 (dd, J = 9.0, 7.5 Hz, 1H, H7α), 4.15 (d, J = 7.5 Hz, 1H, H20β), 4.34 (d, J = 7.5 Hz, 1H, H20α), 4.61 (d,J = 12.0 Hz, 1H, PhC$\underline{H}_2$O), 4.72 (d, J = 12.0 Hz, 1H, PhC$\underline{H}_2$O), 4.81 (d, J = 7.0 Hz, 1H, OCH_2O), 4.92 (d, J = 7.0 Hz, 1H, OCH_2O), 4.93 (br d, J = 6.5 Hz, 1H, H5α), 5.05 (br t, J = 6.5 Hz, 1H, H13β), 5.91 (d, J = 6.0 Hz, 1H, H2β), 7.28 (m, 1H, PhC$\underline{H}_2$O), 7.35 (m, 4H, PhC$\underline{H}_2$O), 7.50 (m, 2H, PhCOO -*m*), 7.62 (m, 1H, PhCOO -*p*), 8.13 (m, 2H, PhCOO -*o*)

Hydroxyketone 33. To a THF (1.3 mL) solution of 32 (P_7 = BOM, P_{13} = TBS) (16.2 mg, 0.02 mmol) at -78 °C was added 4 equivalents of a 0.24M *t* -BuOK solution in THF (0.33 mL, 0.08 mmol.). The solution was warmed to -20 °C for 40 min and then briefly warmed to 0°C before being cannulated into a 0°C THF (1.3 mL) suspension of benzeneseleninic anhydride (57 mg, 0.16 mmol.). The reaction was stirred for 40 min. at 0 °C before being diluted with 20 mL of ethyl acetate and poured into 50 mL of aqueous saturated $NaHCO_3$. The organic layer was then washed with 50 mL of aqueous saturated $Na_2S_2O_3$ followed by 50 mL of aqueous saturated $NaHCO_3$. The organic layer was then dried with Na_2SO_4, filtered and evaporated to give 18.8 mg of the hydroxyketone as an oil. To a THF (1.3 mL) solution of the crude hydroxyketone (18.8 mg) was

added 0.33 mL of a 0.24M solution of *t*-BuOK (0.08 mmol) at -78 °C. The reaction was stirred 20 min. and then 0.25 mL of a 0.8M AcOH/THF solution was added at -78 °C and stirred 5 min. The mixture was diluted with 20 mL of ethyl acetate and was poured into 50 mL of aqueous saturated $NaHCO_3$. The organic layer was then dried with Na_2SO_4, filtered and evaporated to give 18.6 mg of a yellow solid which was then plug filtered through silica gel with 2% ethyl acetate/hexanes followed by 30% ethyl acetate/hexanes to give 15.9 mg of **33** (P_7 = BOM, P_{13} = TBS) (96% yield).

33 (P_7 = BOM, P_{13} = TBS): m.p.: 234-236°C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 3H, TBS CH_3), 0.15 (s, 3H, TBS CH_3), 0.95 (s, 9H, TBS t-Bu), 1.11 (s, 3H, CH_3 16), 1.18 (s, 3H, CH_3 17), 1.59 (s, 1H, OH1), 1.82 (s, 3H, CH_3 18), 1.89 (ddd, *J* = 2.1, 12.4, 14.4 Hz, 1H, H6β), 1.97 (d, *J* = 2.0 Hz, 3H, CH_3 18), 2.14 (dd, *J* = 8.6, 15.4 Hz, 1H, H14β), 2.21 (dd, *J* = 8.9, 15.4 Hz, 1H, H14α), 2.29 (s, 3H, Ac), 2.70 (ddd, *J* = 6.5, 9.6, 14.4 Hz, 1H, H6α), 3.93 (d, *J* = 6.9 Hz, 1H, H3α), 4.17 (d, *J* = 8.6 Hz, 1H, H20β), 4.28 (d, *J* = 2.4 Hz, 1H, OH10β), 4.31 (dd, *J* = 6.5, 12.4 Hz, 1H, H7α), 4.32 (d, *J* = 8.6 Hz, 1H, H20α), 4.45 (d, *J* = 12.2 Hz, 1H, $PhC\underline{H_2}O$), 4.60 (d, *J* = 12.2 Hz, 1H, $PhC\underline{H_2}O$), 4.60 (d, *J* = 7.3 Hz, 1H, OCH_2O), 4.73 (d, *J* = 7.3 Hz, 1H, OCH_2O), 4.97 (dd, *J* = 2.1, 9.6 Hz, 1H, H5α), 5.01 (ddd, *J* = 2.0, 8.6, 8.9 Hz, 1H, H13β), 5.35 (d, *J* = 2.4 Hz, 1H, H10α), 5.64 (d, *J* = 6.9 Hz, 1H, H2β), 7.3 (m, 5H, $\underline{Ph}CH_2$), 7.49 (tt, *J* = 1.7, 7.9 Hz, 2H, PhCOO -*m*), 7.61 (tt, *J* = 1.7, 7.6 Hz, 1H, PhCOO -*p*), 8.10 (dd, *J* = 1.2, 7.9 Hz, PhCOO -*o*).

33 (P_7 = MOP, P_{13} = TBS): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 3H, TBS CH_3), 0.15 (s, 3H, TBS CH_3), 0.95 (s, 9H, TBS t-Bu), 1.00 (s, 3H, CH_3 16), 1.09 (s, 3H, CH_3 17), 1.23 (s, 3H, MOP CH_3), 1.37 (s, 3H, MOP CH_3), 1.58 (s, 1H, OH1), 1.79 (s, 3H, CH_3 19), 1.90 (ddd, *J* = 2.6, 8.8, 13.7 Hz, 1H, H6β), 2.04 (s, 3H, CH_3 18), 2.13 (dd, *J* = 8.8, 15.5 Hz, 1H, H14β), 2.22 (dd, *J* = 8.8, 15.5 Hz, 1H, H14α), 2.29 (s, 3H, OAc), 2.79 (ddd, 6.3, 9.9, 14.8 Hz, 1H, H6α), 3.17 (s, 3H, MOP OCH_3), 3.90 (d, *J* = 7.1 Hz, 1H, H3α), 4.16 (d, *J* = 8.2 Hz, 1H, H20α), 4.25 (d, *J* = 2.2 Hz, 1H, OH4), 4.32 (d, *J* = 8.8 Hz, 1H, H20β), 4.41 (dd, *J* = 6.6, 11.0 Hz, 1H, H7α), 4.94 (dd, *J* = 2.2, 9.9 Hz, 1H, H5α), 5.03 (ddd, *J* = 1.1, 8.2, 8.8 Hz, 1H, H13β), 5.20 (d, *J* = 6.2 Hz, 1H, H10α), 5.60 (d, *J* = 7.2 Hz, 1H, H2β), 7.48 (t, *J* = 7.7 Hz, 2H, PhCOO-*m*), 7.61 (t, *J* = 7.7 Hz, 1H, PhCOO -*p*), 8.10 (d, *J* = 7.1 Hz, 2H,

PhCOO-*o*).

Acetate 34. To a pyridine (0.1 mL) solution of 33 (P_7 = BOM, P_{13} = TBS) (15.9 mg, 0.02 mmol) and DMAP (1.2 mg, 0.01 mmol) at room temperature was added acetic anhydride (38 μL, 0.4 mmol) and the reaction stirred 19 h. The mixture was then diluted with 20 mL of ethyl acetate and poured into 50 mL of aqueous saturated $NaHCO_3$. The organic layer was dried with Na_2SO_4, filtered and evaporated to give 18.1 mg of crude product. The material was plug filtered through silica gel with 20% ethyl acetate/hexanes to give 16.8 mg of 34 (P_7 = BOM, P_{13} = TBS) (100% yield).

34 (P_7 = BOM, P_{13} = TBS): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 3H, TBS Me), 0.16 (s, 3H, TBS Me), 0.95 (s, 9H, TBS t-Bu), 1.17 (s, 3H, CH_3 17), 1.18 (s, 3H, CH_3 16), 1.63 (s, 1H, OH1), 1.76 (s, 3H, CH_3 19), 1.99 (ddd, *J* = 2.1, 10.6, 14.7 Hz, 1H, H6β), 2.04 (d, *J* = 1.0 Hz, 3H, CH_3 18), 2.17 (dd, *J* = 8.6, 15.1 Hz, 1H, H14β), 2.19 (s, 3H, AcO10), 2.24 (dd, *J* = 8.6, 15.1 Hz, 1H, H14α), 2.28 (s, 3H, AcO4), 2.88 (ddd, *J* = 6.5, 9.8, 14.7 Hz, 1H, H6α), 3.87 (d, *J* = 7.0 Hz, 1H, H3α), 4.15 (d, *J* = 8.2 Hz, 1H, H20β), 4.24 (dd, *J* = 6.5, 10.6 Hz, 1H, H7α), 4.31 (d, *J* = 8.2 Hz, 1H, H20α), 4.44 (d, *J* = 12.0 Hz, 1H, $PhC\underline{H}_2O$), 4.68 (d, *J* = 12.0 Hz, 1H, $PhC\underline{H}_2O$), 4.85 (s, 2H, OCH_2O), 4.95 (dd, *J* = 2.1, 9.8 Hz, 1H, H5α), 5.65 (d, *J* = 7.0 Hz, 1H, H2β), 6.39 (s, 1H, H10α), 7.30 (m, 5H, $PhCH_2$), 7.49 (tt, *J* = 1.4, 8.2 Hz, 2H, PhCOO -*m*), 7.61 (tt, *J* = 1.4, 7.2 Hz, 1H, PhCOO -*p*), 8.05 (dd, *J* = 1.2, 8.2 Hz, 1H, PhCOO -*o*), IR ($CHCl_3$) υ 3600, 3050, 2975, 2880, 1750, 1730, 1460, 1379, 1250, 1100, 1020, 860 cm^{-1}.

34 (P_7=P_{13}=TES): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.57 (q, *J* = 7.7 Hz, 6H, TES CH_2), 0.67 (q, *J* = 7.7 Hz, TES CH_2), 0.92 (t, *J* = 7.7 Hz, 9H, TES CH_3), 1.01 (t, *J* = 7.7 Hz, 9H, TES CH_3), 1.11 (s, 3H, CH_3 17), 1.19 (s, 3H, CH_3 19), 1.61 (s, 1H, OH1), 1.67 (s, 3H, CH_3 16), 1.86 (ddd, *J* = 2.2, 10.4, 14.3 Hz, 1H, H6β), 2.11 (d, *J* = 1.1 Hz, 3H, CH_3 18), 2.12 (m, 1H, H14β), 2.17 (s, 3H, OAc10), 2.23 (dd, *J* = 7.6, 14.9 Hz, 1H. H14α), 2.28 (s, 3H, OAc4), 2.51 (ddd, *J* = 6.9, 9.6, 14.3 Hz, 1H, H6α), 3.82 (d, *J* = 7.2 Hz, 1H, H3α), 4.14 (d, *J* = °.3 Hz, 1H, H20β), 4.30 (d, *J* = 8.3 Hz, 1H, H20α), 4.48 (dd, *J* = 6.6, 10.4 Hz, 1H, H7α), 4.92 (dd, *J* = 7.7, 8.8 Hz, 1H, H5α), 4.96 (d, *J* = 8.2 Hz, 1H, H13β), 5.63 (d, *J* = 6.6 Hz, 1H,

H2α), 6.47 (s, 1H, H10α), 7.47 (t, J = 7.1 Hz, 2H, PhCOO -*m*), 7.60 (t, J = 7.1 Hz, PhCOO -*p*), 8.10 (d, J = 7.1 Hz, PhCOO -*o*).

Diol 35. A solution of 34 (P_7 = BOM, P_{13} = TBS) (16.3 mg, 0.0199 mmol) in THF (0.5 mL) was added to tris(diethylamino)sulfoniumdifluorotrimethylsilicate (TASF) (37 mg, 0.134 mmole) at room temperature under nitrogen atmosphere. The solution was stirred for 40 min, diluted with ethyl acetate, poured into 20 mL of a saturated aqueous $NaHCO_3$ solution and extacted with $CHCl_3$ (30 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 16 mg of a pale yellow oil, which was filtered through a pad of silica gel using 70 % ethyl acetate/hexane as eluent. The filtrate was concentrated to yield 13.5 mg (94 %) of 7-BOM BIII (35).

35 (P_7=BOM) mp. 224-225 °C, ^{1}H NMR (500 MHz, $CDCl_3$), δ 1.08 (s, 3H, CH_3 17), 1.18 (s, 3H, CH_3 16), 1.61 (s, 1H, OH1), 1.77 (s, 3H, CH_3 19), 1.99 (ddd, J = 2, 10.5, 14.5 Hz, 1H, H6β), 2.02(d, J = 5 Hz, 1H, OH13), 2.10 (d, J = 1.5 Hz, 3H, CH_3 18), 2.20 (s, 3H, AcO), 2.28 (s, 3H, AcO), 2.27-2.29 (m, 2H, H14), 2.89 (ddd, J = 7, 10, 16.5 Hz, 1H, H6α), 3.94 (d, J = 7 Hz, 1H, H3), 4.16 (dd, J = 1, 8.5 Hz, 1H, H20β), 4.24 (dd, J = 6.5, 10.5 Hz, 1H, H7), 4.31 (d, J = 8 Hz, 1H, H20α), 4.45 (d, J = 12.0 Hz, 1H, $OC\underline{H}_2Ph$), 4.67 (d, J = 12.0 Hz, 1H, $OC\underline{H}_2Ph$), 4.84 (d, J = 5 Hz, 1H, OCH_2O), 4.86 (d, J = 5 Hz, 1H, OCH_2O), 4.87 (m, 1H, H13β), 4.95 (dd, J = 2.0, 9.5 Hz, 1H, H5α), 5.63 (d, J = 7 Hz, 1H, H2β), 6.40 (s, 1H, H10α), 7.30 (m, 5H, $\underline{Ph}CH_2$), 7.48 (m, 2H, PhCOO -*m*), 7.61 (m, 1H, PhCOO -*p*), 8.10 (2H, m, PhCOO -*o*). ^{13}C NMR ($CDCl_3$) δ (ppm) 10.3, 14.9, 20.0, 20.7, 22.4, 26.6, 35.3, 38.4, 42.7, 47.2, 57.4, 67.8, 69.9, 74.6, 75.8, 76.4, 78.7, 80.3, 80.3, 80.9, 84.4, 96.7, 127.7, 127.9, 128.5, 128.8, 129.6, 130.3, 132.4, 133.8, 138.0, 144.4, 167.3, 169.8, 171.0, 203.0. IR ($CHCl_3$) υ 1720, 1460 cm^{-1}. Anal. Calcd. for $C_{39}H_{46}O_{12}$: C, 66.28; H, 6.56. Found C, 66.09; H, 6.59.

7-BOM-Taxol. To a solution of 7-BOM baccatin III (35) (13.2 mg, 0.018 mmol) in 0.25 mL of THF at -45 °C was added dropwise 21 μL of a 1.03 M solution of lithium bis(trimethylsilyl)amide in THF. After 1h at -45 °C, a solution of (S)-*cis*-1-benzoyl-3-triethylsilyloxy-4-azetidin-2-one (15

mg, 0.039 mmol) in 0.25 mL of THF was added dropwise to the mixture. The solution was warmed to 0 °C and kept at that temperature for 1 h before 0.2 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60% ethyl acetate / hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 20.2 mg of crude (2'R,3'S)-2'-triethylsilyl-7-BOM taxol.

To a solution of 20.2 mg (0.018 mmol) of (2'R,3'S)-2'-triethylsilyl-7-BOM taxol in 0.8 mL of acetonitrile and 0.3 mL of pyridine at 0 °C was added 0.10 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 1 h and then partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 17.7 mg of material which was purified by flash chromatography to give 15.4 mg (86%) of 7-BOM-taxol.

7-BOM-Taxol: m.p 169-172 °C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, J = 7.1 Hz,2H, benzoate *ortho*), 7.76 (d, J=7.1 Hz,1H, benzamide *ortho*), 7.61-7.26 (m, 11 H, aromatic), 7.06(d, J = 8.8 Hz, 1H, NH), 6.33 (s, 1H, H10), 6.17 (dd, J = 8.8, 8.8 Hz, 1H, H13), 5.79 (dd, J = 8.8, 2.2 Hz, 1H, H3'), 5.67 (d, J = 6.6 Hz, 1H, H2b), 4.91 (d, J=8.8 Hz,1H, H5), 4.87-4.77(m, 3H, H2', OCH2Ph),4.67(d, J=12 Hz, OCH2O) 4.43(d, J=12 Hz, OCH2O), 4.30 (d, J = 8.2 Hz, 1H, H20a), 4.19 (d, J = 8.2 Hz, 1H, H20b), 4.15 (m, 1H, H7), 3.70 (d, J = 6.6 Hz, 1H, H3), 3.61 (d, J = 2.5 Hz, 1H, 2'OH), 2.85 (m, 1H, H6a), 2.35 (s, 3H, 4Ac), 2.30 (m, 2H, H14), 2.19 (s, 3H, 10Ac), 2.05 (m, 1H, H6b), 1.78 (br s, 6H, Me18,Me19), 1.72 (s, 1H, 1OH), 1.19 (br s, 6H, Me16, Me17). Anal. Calcd. for $C_{55}H_{59}O_{15}$x$0.5H_2O$: C, 67.20; H, 6.15. Found C, 67.08; H, 6.16.

Taxol. To a suspension of 10% Pd on carbon (50 mg) in ethanol (0.6 mL) saturated with hydrogen at room temperature was added a solution of 7-BOM-taxol (14.4 mg, 0.0148 mmol) in ethanol (0.2 mL x 4). The reaction mixture was refluxed for 45 min under hydrogen and then filtered through silica gel eluting with ethyl acetate. The solvent was evaporated under reduced pressure to give 11.9 mg of taxol (94%) as colorless needles, which exhibited spectra identical with an authentic sample of taxol.

Taxol: mp. 210-212 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s,3H, CH_3 16), 1.24 (s, 3H, CH_3 17), 1.68 (s, 3H, CH_3 19), 1.75 (s, 1H, OH1), 1.79 (s, 3H, CH_3 18), 1.90 (ddd, J = 14.6,

11.0, 2.3 Hz, 1 H, H6β), 2.26 (s, 3H, AcO10), 2.33 (dd, J=15.4, 8.9 Hz, 1H, H14β), 2.38 (dd, J=15.4, 8.9 Hz, 1H, H14α), 2.41 (s, 3H, AcO4), 2.46 (d, J=4.1 Hz, 1H, OH7), 2.57 (ddd, J=10.0,14.6,6.5 Hz, 1H, H6α), 3.54 (d, J=5.0 Hz, 1H, OH2'), 3.82 (d,J=6.9 Hz, 1H, H3α), 4.22 (d, J=8.5 Hz, 1 H, H20α), 4.32 (d, J=8.5 Hz, 1 H, H20β), 4.42 (ddd, J=11.0, 6.5, 4.1 Hz, 1 H, H7α), 4.81 (dd, J= 5.0, 2.5 Hz, 1 H, H2'), 4.96 (dd, J=10.0, 2.3 Hz, 1H, H5α), 5.69 (d, J=6.9 Hz, 1 H, H2β), 5.81 (dd, J=8.7, 2.5 Hz, 1 H, H3'), 6.25 (dd, J=8.9, 8.9 Hz, 1 H, H13β), 6.29 (s, 1H, H 10α), 6.98 (d, J= 8.7 Hz, 1H, NH),7.37 (m, 1H, PhCON -*p*), 7.46 (m, 9 H, Ph 3', PhCOO 2' -*m*, PhCON -*m*), 7.62 (m, 1H, PhCOO -*p*), 7.76 (br d, J =8.7 Hz, 1H, PhCON -*o*), 8.16 (br d, J=7.3 Hz, 1 H, PhCOO -*o*). IR ($CHCl_3$) υ 1730, 1650 cm^{-1}.

10-Deacetyl baccatin III (36). To a mixture of ketone 33 (P_7 = MOP, P_{13} = TES) (2.2 mg, 0.003 mmol) in pyridine (30 μL, 0.36 mmol) and acetonitrile (20 μL) at 0 °C was added 48% aqueous HF (12 μL, 0.32 mmol) and the solution was then warmed to room temperature and stirred for 36 hours. The mixture was then diluted with 2 mL of ethyl acetate and poured in to a separatory funnel containing 30 mL of aqueous saturated Na_2CO_3 and 20 mL ethyl acetate. The aqueous layer was extracted twice with 20 mL of ethyl acetate and the organic layers were combined, dried with Na_2SO_4, filtered, and concentrated to give 2.7 mg of a yellow oil. The material was purified by plug silica gel column chromatography by eluting with a 50% ethyl acetate/hexanes mixture followed by ethyl acetate to give 1.5 mg of 36, which exhibited spectra identical with an authentic sample of 10-DAB.

Baccatin III (37). To a mixture of ketone 34 (P_7 = MOP) (2.1 mg, 0.003 mmol) in pyridine (30 μL, 0.36 mmol) and acetonitrile (20 μL) at 0 °C was added 48% aqueous HF (12 μL, 0.32 mmol) and the solution was then warmed to room temperature and stirred for 36 hours. The mixture was then diluted with 2 mL of ethyl acetate and poured in to a separatory funnel containing 30 mL of aqueous saturated Na_2CO_3 and 20 mL ethyl acetate. The aqueous layer was extracted twice with 20 mL of ethyl acetate and the organic layers were combined, dried with Na_2SO_4, filtered, and concentrated to give 2.7 mg of a yellow oil. The material was purified by plug silica gel column

chromatography by eluting with an ethyl acetate/hexanes mixture to give 1.7 mg of **37**, which exhibited spectra identical with an authentic sample of baccatin III.

REACTION SCHEME A'

Hydroxyketone **19**. To a vigorously stirred solution of ketone **18** (P_7=MOP) (181 mg, 0.265 mmol) in THF (2.2 mL) under nitrogen at -78 °C was added dropwise down the side of the flask 2.13 mL of a 0.2 M solution (0.426 mmol) of LDA in THF. After 10 min, a solution of 116 mg of (S)-camphorsulfonyloxaziridine (116 mg, 0.396 mmol) in 1.5 mL THF was added dropwise down the side of the flask. The reaction mixture was cooled to -40 °C and, after stirring 1 h, 2 mL of a saturated aqueous $NaHCO_3$ solution was added. The reaction mixture was diluted with 50 mL of 30% ethyl acetate in hexanes and washed with 20 mL of a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting oil was filtered through silica gel with 30% ethyl acetate in hexanes and concentrated to give 210 mg of a colorless oil. This material was purified by radial chromatography, eluting with 25% ethyl acetate in hexanes to yield 150 mg (81%) 5β-hydroxyketone **19** as a white solid, 15 mg (8%) returned starting ketone **18** and 10 mg (5%) of the corresponding 5α-hydroxyketone.

19 (P_7=MOP): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H, TBS CH_3), 0.12 (s, 3H, TBS CH_3), 0.62 (q, J = 8.2 Hz, 6H, TES CH_2), 0.90 (s, 9H, TBS t-Bu), 0.96 (t, J = 8.2 Hz, 9H, TES CH_3), 1.05 (s, 3H, CH_3 19), 1.19 (s, 3H, CH_3 17), 1.33 (s, 3H, CH_3 16), 1.35 (s, 3H, MOP CH_3), 1.43 (s, 3H, MOP CH_3), 1.67 (dd, J = 5.0, 14.7 Hz, 1H, H9β), 1.87 (m, 1H, H6β), 2.12 (dd, J = 4.1, 15.1 Hz, 1H, H14α), 2.14 (d, J = 1.4 Hz, 3H, CH_3 18), 2.23 (dd, J = 7.3, 14.7 Hz, 1H, H9α), 2.55 (dd, J = 9.2, 15.1 Hz, 1H, H14β), 2.76 (ddd, J = 3.7, 7.3, 13.7 Hz, 1H, H6α), 3.22 (s, 3H, MOP OCH_3), 3.24 (d, J = 4.1 Hz, 1H, OH5), 3.28 (d, J = 6.0 Hz, 1H, H3α), 3.83 (dd, J = 3.7, 9.2 Hz, 1H, H7α), 4.06 (ddd, J = 4.1, 7.3, 7.3 Hz, 1H, H5α), 4.46 (dd, J = 5.0, 7.3 Hz, 1H, H10β), 4.53 (d, J = 6.0 Hz, 1H, H2β), 4.63 (dd, J = 2.8, 9.2 Hz, 1H, H13β).

Ketone **20**. To a vigorously stirred solution of 5-hydroxy-4-ketone **19** (P_7=MOP) (420 mg, 0.602 mmol) in CH_2Cl_2 (20 mL) and triethylamine (1.18 mL, 8.5 mmol) und r nitrogen at O °C

was added trimethylsilylchloride (0.40 mL, 3.3 mmol). After 0.5 h, the reaction mixture was quenched with 5 mL of a saturated aqueous $NaHCO_3$ solution and extracted with 50 mL $CHCL_3$. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 453 mg (98%) of ketone **20** as a colorless oil. This material was used without further purification.

20 (P_7=MOP): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 6H, TBS CH_3), 0.12 (s, 9H, TMS CH_3), 0.59 (q, J = 7.8 Hz, 6H, TES CH_2), 0.94 (s, 9H, TBS t-Bu), 0.96 (t, J = 7.8 Hz, 9H, TES CH_3), 1.23 (s, 3H, CH_3 17), 1.32 (s, 3H, CH_3 19), 1.33 (s, 3H, MOP CH_3), 1.35 (s, 3H, CH_3 16), 1.37 (s, 3H, MOP CH_3), 1.86 (m, 3H, H6β, H9α, H9β), 2.05 (d, J = 1.4 Hz, 3H, CH_3 18), 2.43 (d, J = 3.7 Hz, 1H, H14β), 2.45 (d, J = 4.6 Hz, 1H, H14α), 2.59 (ddd, J = 6.0, 8.2, 14.2 Hz, 1H, H6α), 2.84 (d, J = 6.0 Hz, 1H, H3α), 3.21 (s, 3H, MOP OMe), 3.51 (dd, J = 6.0, 11.0 Hz, 1H, H7α), 3.94 (dd, J = 4.1, 8.2 Hz, 1H, H5α), 4.38 (dd, J = 5.0, 8.7 Hz, 1H, H10β), 4.54 (d, J = 6.0 Hz, 1H, H2β), 4.74 (dd, J = 6.4, 6.4 Hz, 1H, H13β).

Diol **21**. To a stirred solution of ketone **20** (P_7=MOP) (453 mg, 0.588 mmol) in THF (23 mL) under nitrogen at -78 °C was added dropwise 1.95 mL of a 3 M solution of MeMgBr in ether (5.85 mmol). The reaction mixture was stirred for 5.5 h, poured into 100 mL of a saturated aqueous $NaHCO_3$ solution and extracted with three 100 mL portions of $CHCl_3$. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield 453 mg of the hydroxy trimethylsilyl ether as a colorless oil. This material was used without further purification.

To a stirred solution of the trimethylsilyl ether (453 mg) in pyridine (8 mL) and acetonitrile (8 mL) at 0 °C was added 0.8 mL of a 48% aqueous HF solution. After stirring 20 min, the resulting mixture was poured into 100 mL of a saturated aqueous $NaHCO_3$ solution and extracted with three 150 mL portions of $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield 422 mg of diol **21**. This material used without further purification.

21 (P_7=MOP): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 3H, TBS CH_3), 0.10 (s, 3H, TBS CH_3), 0.56 (q, J = 7.7 Hz, 6H, TES CH_2), 0.90 (s, 9H, TBS t-Bu), 0.93 (t, J = 7.7 Hz, 9H, TES

CH_3), 1.16 (s, 3H, CH_3 17), 1.25 (s, 3H, CH_3 16), 1.29 (s, 3H, CH_3 19), 1.31 (s, 3H, CH_3 20), 1.38 (s, 3H, MOP CH_3), 1.46 (s, 3H, MOP CH_3), 1.81 (d, J = 3.8 Hz, 1H, H3α), 1.86 (d, J = 9.9 Hz, 1H, H9β), 1.90 (dd, J = 6.1, 8.3 Hz, 1H, H9α), 1.96 (s, 3H, CH_3 18), 2.12 (ddd, J = 3.3, 3.3, 10.4 Hz, 1H, H6α), 2.30 (m, 1H, H6β), 2.42 (dd, J = 3.9, 15.4 Hz, 1H, H14α), 2.61 (dd, J = 9.3, 15.4 Hz, 1H, H14β), 2.81 (s, 1H, OH4), 3.04 (m, 1H, OH5), 3.40 (dd, J = 3.9, 15.8 Hz, 1H, H7α), 4.28 (dd, J = 6.6, 8.2 Hz, 1H, H10β), 4.62 (dd, J = 1.6, 7.8 Hz, 1H, H13β), 4.66 (d, J = 3.8, 1H, H2β).

Acetate 22. To a stirred solution of diol 21 (P_7=MOP) (470 mg, 0.66 mmol) in pyridine (12 mL) under nitrogen at room temperature was added acetic anhydride (4.5 mL). After 11 h, the reaction mixture was diluted with 50 mL of $CHCl_3$, then poured into 50 mL of saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted with $CHCl_3$ then the combined extracts were washed with brine, dried with Na_2SO_4 and filtered. Concentration of the filtrate under vacuum yielded 470 mg (94% from 20) of crude material which was pure acetate 22 by ^{1}H NMR and TLC analysis.

22 (P_5=Ac, P_7=MOP): ^{1}H NMR (500MHz, $CDCl_3$) δ 0.10 (s, 3H, TBS CH_3), 0.13 (s, 3H, TBS CH_3), 0.59 (q, J = 7.8 Hz, 6H, TES CH_2), 0.94 (s, 9H, TBS t-Bu), 0.95 (t, J = 7.8 Hz, 9H, TES CH_3), 1.18 (s, 3H, CH_3 17), 1.30 (s, 3H, CH_3 16), 1.32 (s, 3H, CH_3 19), 1.33 (s, 6H, CH_3 20, MOP CH_3), 1.41 (s, 3H, MOP CH_3), 1.91 (d, J = 3.4 Hz, 1H, H3α), 1.94 (m, 2H, H9, H9), 2.00 (d, J = 1.5 Hz, 3H, CH_3 18), 2.06 (ddd, J = 3.9, 3.9, 11.7 Hz, 1H, H6α), 2.10 (s, 3H, OAc), 2.14 (dd, J = 11.7, 23.9 Hz, 1H, H6β), 2.38 (dd, J = 3.9, 15.1 Hz, 1H, H14α), 2.63 (dd, J = 9.3, 15.1 Hz, 1H, H14β), 2.78 (d, J = 1.5 Hz, 1H, OH4), 3.20 (s, 3H, OMe CH_3), 3.38 (dd, J = 3.9, 11.7 Hz, 1H, H7α), 4.30 (dd, J = 4.9, 10.3 Hz, 1H, H10β), 4.50 (ddd, J = 1.5, 3.9, 12.2 Hz, 1H, H5α), 4.64 (dd, J = 1.5, 1.5 Hz, 1H, H13β), 4.66 (d, J = 3.4 Hz, 1H, H2β).

Olefin 23. To a stirred solution of alcohol 22 (P_5=Ac, P_7=MOP) (26 mg, 0.034 mmol) in CH_2Cl_2 (1.48 mL) and pyridine (0.37 mL) under nitrogen at 10 °C was added $SOCl_2$(0.037 mL, 5.1 mmol) ver a period of three minutes. The mixture was warmed to room temperature and

stirred for 2.3 h then diluted with $CHCl_3$ and poured into saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted with $CHCl_3$ and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and filtered. Concentration of the filtrate under vacuum yielded 24 mg of crude material which was purified by silica gel chromatography to give 13 mg (52%) of a 4:1 mixture of 7-MOP-*exo;endo* cyclic olefins and 6 mg (27%) of a 4:1 mixture of 7-hydroxy-*exo;endo* cyclic olefins.

23 (P_5=Ac, P_7=MOP): ^1H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 3H, TBS CH_3), 0.12 (s, 3H, TBS CH_3), 0.59 (q, *J* = 7.9, 6H, TES CH_2), 0.93 (s, 9H, TBS t-Bu), 0.96 (t, *J* = 7.9, 9H, TES CH_3), 1.21 (s, 3H, CH_3 17), 1.30 (s, 3H, CH_3 19), 1.32 (s, 3H, MOP CH_3), 1.34 (s, 3H, MOP CH_3), 1.37 (s, 3H, CH_3 16), 1.72 (m, 2H, H6β, H9β), 1.89 (dd, *J* = 3.8, 13.4 Hz, 1H, H9β), 2.03 (d, *J* = 1.37 Hz, 3H, CH_3 18), 2.05 (s, 3H, OAc CH_3), 2.33 (dd, *J* = 5.1, 15.4 Hz, 1H, H14α), 2.47 (m, 2H, H6α, H14β), 3.06 (d, *J* = 5.8 Hz, 1H, H3α), 3.20 (s, 3H, MOP OMe), 3.38 (dd, *J* = 6.9, 11.0 Hz, 1H, H7α), 4.37 (dd, *J* = 3.8, 11.0 Hz, 1H, H10β), 4.53 (d, *J* = 5.8 Hz, 1H, H2β), 4.74 (m, 1H, H13β), 5.15 (s, 1H, H20E), 5.21 (d, *J* = 1.37 Hz, 1H, H20Z), 5.36 (d, *J* = 9.3 Hz, 1H, H5α).

Diol **24**. To a stirred solution of a 4:1 mixture of the *exo,endo*cyclic olefins **23** (P_5=Ac, P_7=MOP) (249 mg, 0.337 mmol) in pyridine (4.6 mL) under nitrogen at 0 °C was added 2.35 mL of a 0.157 M solution (0.368 mmol) of OsO_4 in THF. After 1 h, $NaHSO_3$ was added along with 6.2 mL of water and the mixture was stirred for 1 h at room temperature. The mixture was then diluted with ethyl acetate and poured into saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield 281 mg of crude material which was purified by silica gel chromatography, eluting with 50% ethyl acetate/hexane to yield 190 mg (73%) of pure diol **24** and 48 mg (19%) of the enol acetate.

24 (P_5=Ac, P_7=MOP): ^1H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 3H, TBS CH_3), 0.11 (s, 3H, TBS CH_3), 0.60 (dq, *J* = 1.5, 7.8 Hz, 6H, TES CH_2), 0.87 (s, 3H, CH_3 19), 0.93 (s, 9H, TBS t-Bu), 0.95 (t, *J* = 7.8 Hz, 9H, TES CH_3), 1.20 (s, 3H, CH_3 17), 1.31 (s, 3H, CH_3 16), 1.33 (s, 3H, MOP CH_3), 1.47 (s, 3H, MOP CH_3)1.54 (dd, *J* = 12.3, 25.0 Hz, 1H, H6β), 1.63 (dd, *J* =

5.5, 15.1 Hz, 1H, H9β), 2.05 (s, 3H, OAc), 2.15 (s, 3H, CH_3 18), 2.26 (m, 2H, H9α, OH20) 2.37 (dd, J = 9.2, 14.7 Hz, 1H, H14β), 2.46 (ddd, J = 4.8, 4.8, 13.4 Hz, 1H, H6α), 2.69 (d, J = 4.5 Hz, 1H, H3α), 3.18 (s, 3H, MOP CH_3), 3.28 (dd, J = 3.8, 14.7 Hz, 1H, H14α), 3.76 (dd, J = 4.0, 11.6 Hz, 1H, H7α), 3.84 (m, 2H, H20, H20), 3.95 (s, 1H, OH4), 4.42 (dd, J = 5.1, 5.8 Hz, 1H, H10β), 4.44 (d, J = 4.1 Hz, 1H, H2β), 4.63 (dd, J = 4.1, 12.3 Hz, 1H, H5α), 4.67 (dd, J = 4.1, 9.2 Hz, 1H, H13β).

24 (P_7=BOM): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9 (s, 3H, TBS CH_3), 0.10 (s, 3H, TBS CH_3), 0.58 (q, J =7.9Hz, 2H, TES CH_2), 0.83 (s, 3H, CH_3 19), 0.92 (s, 9H, TBS t-Bu), 0.93(t, J = 7.9 Hz, TES CH_3), 1.20 (s, 3H, CH_3 17), 1.33 (s, 3H, CH_3 16), 1.58 (q, J = 13.2Hz, 1H, H6β), 1.71 (dd, J = 10.4, 5.5 Hz, H9β), 2.04(s, 3H, OAc), 2.17 (br s, 3H, CH_3 18), 2.20 (dd, J = 10.4, 3.8 Hz, 1H, H9α), 2.35 (dd, J = 14.8, 9.1 Hz, 1H, H14β), 2.43 (dt, J = 13.2, 5.0 Hz, 1H, H6α), 2.80 (d, J = 4.6 Hz, 1H, H3α), 3.31 (dd, J = 4.4, 14.8 Hz, 1H, H14α), 3.71 (dd, J = 4.9, 13.0 Hz, 1H, H7α), 3.83 (m, 2H, H20), 3.98(s, 1H, OH1), 4.46(d, J = 4.8 Hz, 1H, H2β), 4.48 (m, 1H, H10β), 4.51(d, J = 12.1 Hz, 1H, Ph$C\underline{H}_2$O), 4.64 (dd, J = 13.2, 5.0 Hz, 1H, H5α), 4.66 (m, 1H, H13β), 4.70 (d, J = 12.1 Hz, 1H, Ph$C\underline{H}_2$O), 4.83 (d, J = 7.1 Hz, 1H, OCH_2O), 4.94 (d, J =7.1 Hz, 1H, OCH_2O), 7.33(m, 5H, Ph).

Triol **25**. To a stirred solution of acetoxydiol **24** (P_5=Ac, P_7=MOP) (26.5 mg, 0.035 mmol) in anhydrous methanol (0.9 mL) at -5 °C under nitrogen was added 0.060 mL of a 0.166 M (0.01 mmol) methanolic solution of sodium methoxide. After 2.5 h, the reaction mixture was diluted with 10 mL of ethyl acetate, then poured into 10 mL of a saturated aqueous $NaHCO_3$ solution. The organic phase was washed with 10 mL of a saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 25 mg of pure triol **25** (100%).

25 (P_7=MOP): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 3H, TBS CH_3), 0.11 (s, 3H, TBS CH_3), 0.60 (q, J = 8.06 Hz, 6H, TES CH_2), 0.87 (s, 3H, CH_3 19), 0.94 (s, 9H, TBS t-Bu), 0.95 (t, J = 8.1 Hz, 9H, TES CH_3), 1.19 (s, 3H, CH_3 17), 1.31 (s, 3H, CH_3 16), 1.33 (s, 3H, MOP CH_3), 1.47 (s, 3H, MOP CH_3), 1.59 (dd, J = 11.7, 11.7 HZ, 1H, H6β), 1.62 (dd, J = 5.5, 16.1 HZ, 1H, H9β), 2.11 (d, J = 0.7 Hz, 3H, CH_3 18), 2.24 (dd, J = 5.5, 16.1 Hz, 1H, H9α), 2.38

(dd, J = 9.5, 15.0 Hz, 1H, H14β), 2.45 (ddd, J = 4.4, 4.4, 13.6 Hz, 1H, H6α), 2.60 (d, J = 4.4 Hz, 1H, H3α), 3.21 (s, 3H, MOP OMe), 3.25 (dd, J = 4.4, 15.0 Hz, 1H, H14α), 3.52 (dd, J = 4.4, 12.8 Hz, 1H, H7α), 3.72 (dd, J = 4.4, 11.4 Hz, 1H, H5α), 3.79 (s, 1H, OH4), 3.86 (d, J = 11.0, 1H, H20), 3.93 (d, J = 11.4 Hz, 1H, H20), 4.42 (dd, J = 5.1, 5.1 Hz, 1H, H10β), 4.45 (d, J = 4.4 Hz, 1H, H2β), 4.66 (dd, J = 4.0, 9.2 Hz, 1H, H13β).

p-Methoxybenzylidene acetal **25b**: To a solution of the diol **24** (P_5=Ac, P_7=BOM) (6.5 mg, 0.0079 mmol) and anisaldehyde dimethyl acetal (0.013 ml, 0.076 mmol) stirred in CH_2Cl_2 was added a solution of *p*-toluenesulfonic acid (0.002 ml, 0.1M in THF, 0.0002 mmol). The resulting solution was stirred at room temperature for 15 min then triethylamine (0.1 ml) was added and stirring was continued for 10 min. The mixture was rinsed into 30% ethyl acetate in hexanes (15 ml) then the aqueous phase was extracted with 30% ethyl acetate in hexanes (2 x 5 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and filtered. Concentration of the filtrate under vacuum yielded 12 mg of colorless oil which was purified by silica gel chromatography to yield 6.9 mg (96%) of *p*-methoxybenzylidene acetal **25b** as a 5:1 mixture of diasteromers.

25b (P_5=Ac, P_7=BOM, major diasteromer): ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.05 (s, 3H, TBS CH_3), 0.07 (s, 3H, TBS CH_3), 0.60 (q, J = 7.9Hz, 2H, TES CH_2), 0.78 (s, 3H, CH_3 19) 0.82 (s, 9H, TBS t-Bu), 0.95(t, J = 7.9 Hz, TES CH_3), 1.25 (s, 3H, CH_3 17), 1.37 (s, 3H, CH_3 16), 1.58 (m, H6β), 1.70 (dd, J = 16.8,5.8 Hz, H9β), 1.74 (s, 3H, OAc), 2.26 (s, 3H, CH_3 18), 2.28 (dd, J = 16.8, 1.4 Hz, 1H, H9α), 2.38 (dd, J = 15.1, 9.7 Hz, 1H, H14β), 2.57 (dt, J = 5.1, 9.9 Hz, 1H, H6α) 3.10 (dd, J = 5.1, 14.7 Hz, 1H, H14α), 3.11 (d, J = 4.8 Hz, 1H, H3α), 3.79 (s, 3H, OCH_3), 3.84 (dd, J = 5.0, 11.5 Hz, 1H, H7α), 4.15 (d, J = 8.2 Hz, 1H, H20), 4.20 (d, J = 8.2 Hz, 1H, H20), 4.48(d, J = 12.0 Hz, 1H, $OC\underline{H}_2Ph$), 4.55 (d, J = 4.8 Hz, 1H, H2β), 4.57 (m, 1H, H10β), 4.71 (d, J = 12.0 Hz, 1H, $OC\underline{H}_2Ph$), 4.73 (m, 1H, H13β), 4.78 (dd, J = 12.4, 4.9 Hz, 1H, H5α), 4.84 (d, J = 6.7 Hz, 1H, OCH_2O), 4.99 (d, J = 6.7 Hz, 1H, OCH_2O), 6.05 (s, 1H, acetal CH), 6.80 (d, J = 7.5 Hz, 2H, *p*-MeO<u>Ph</u> -*o*), 7.27-7.36 (m, 7H, *p*-MeOPh -*m* and Ph).

Acetonide **26b**. To a solution of the *p*-methoxybenzylidene acetal **25b** (P_5=Ac, P_7=BOM) (11.5 mg, 0.012 mmol) in 0.4 mL of toluene stirred at 0 °C was added a solution of diisobutylaluminum hydride (0.082 ml, 2.0M in toluene, 0.12 mmol). The resulting solution was stirred for 3.5 h then methanol (0.1 ml) was added. The mixture was diluted with ethyl acetate (5 ml) and stirred with saturated aqueous sodium potassium tartrate for 1.5 hours. The aqueous phase was separated and extracted with ethyl acetate (2 x 10 ml) then the combined extracts were washed with brine and dried with Na_2SO_4. Filtration followed by concentration of the filtrate under vacuum yielded 12 mg of crude material that was purified by silica gel chromatography (30% ethyl acetate in hexanes eluent) to yield 4.7 mg of a mixture of formate acetals, 1.1 mg of 4-MPM-1,2,5,20-tetraol, and 5.2 mg of a mixture of formate *p*-methoxybenzyl ethers.

The mixture of formate acetals was dissolved in methanol (0.1 ml) and 3% aqueous NH_4OH was added. The cloudy mixture was stirred at room temperature for 30 min then rinsed into ethyl acetate over saturated aqueous $NaHCO_3$. The aqueous phase was extracted with ethyl acetate (2 x 10 ml) and the combined extracts were washed with brine, dried over Na_2SO_4, and filtered. Concentration of the filtrate under vacuum yielded a mixture of *p*-methoxybenzylidene acetals. The mixture of acetals was dissolved in toluene (0.4 ml) and the solution was cooled to 0 °C then a solution of diisobutylaluminum hydride (0.02 ml, 2.0M in toluene, 0.08 mmol) was added. The resulting solution was stirred for 3.5 hours then methanol (0.1 ml) was added. The mixture was diluted with ethyl acetate (5 ml) and stirred with saturated aqueous sodium potassium tartrate for 1.5 hours. The aqueous phase was separated and extracted with ethyl acetate (2 x 10 ml) and the combined extracts were washed with brine and dried over Na_2SO_4. Filtration followed by concentration of the filtrate under vacuum yielded 4.5 mg of crude material that was purified by silica gel chromatography (30% ethyl acetate in hexanes eluent) to yield 2.8 mg of 4-MPM-1,2,5,20-tetraol.

The mixture of formate *p*-methoxybenzyl ethers was dissolved in methanol (0.1ml) and 3% aqueous NH_4OH (0.1ml) was added. The cloudy mixture was stirred at room temperature for 30 minutes then rinsed into ethyl acetate over saturated aqueous $NaHCO_3$. The aqueous phase was extracted with ethyl acetate (2 x 10ml) and the combined extracts were washed with brine, dried

over Na_2SO_4, and filtered. Concentration of the filtrate under vacuum yielded 4.8mg of crude material which was purified by silica gel chromatography to yield 3.2mg of 4-MPM-1,2,5,20-tetraol. Total combined yield of 4-MPM-1,2,5,20-tetraol: 68% from **25b**.

4-MPM-1,2,5,20-tetraol : ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 3H, TBS CH_3), 0.06 (s, 3H, TBS CH_3), 0.60 (q, J = 8.0Hz, 2H, TES CH_2), 0.89 (s, 9H, TBS t-Bu), 0.95(t, J = 8.0 Hz, TES CH_3), 0.97 (s, 3H, CH_3 19), 1.22 (s, 3H, CH_3 17), 1.30 (s, 3H, CH_3 16), 1.83 (dd, J = 16.8,5.8 Hz, H9α), 1.91 (q, J = 12.4 Hz, 1H, H6β), 2.12 (m, 2H, H9α and 14β), 2.18 (s, 3H, CH_3 18), 2.55 (m, 2H, H14β and 6α), 2.79 (d, J = 5.3 Hz, 1H, H3α), 2.95 (d, J = 3.0 Hz, 1H, OH5), 3.54 (m, 1H, OH20), 3.66(dd, J = 10.3, 5.3 Hz, 1H, H2β), 3.81 (s, 3H, OCH_3), 3.85 (dd, J = 5.2, 11.6 Hz, 1H, H7α), 3.91 (dt, J = 5.9, 12.4, 1H, H5α), 4.18 (s, 1H, OH1), 4.13 (d, J = 13 Hz, 1H, H20), 4.20 (dd, J = 7.22, 12.9 Hz, 1H, H20), 4.47 (d, J = 11.8 Hz, 1H, $OC\underline{H}_2Ph$), 4.58 (m, 1H, H10β), 4.79 (d, J = 11.8 Hz, 1H, $OC\underline{H}_2Ph$), 4.85 (m, 1H, H13β), 4.87 (d, J = 6.8 Hz, 1H, OCH_2O), 5.01 (d, J = 10.6 Hz, 1H, MPM $C\underline{H}_2$), 5.10 (d, J = 6.8 Hz, 1H, OCH_2O), 5.11(d, J = 10.6 Hz, 1H, MPM $C\underline{H}_2$), 5.49(d, J = 10.5 Hz, 1H, OH2), 6.87 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H, *p*-MeO<u>Ph</u> -*o*), 7.27-7.36 (m, 5H, *p*-MeO<u>Ph</u> -*m* and <u>Ph</u> CH_2).

To a solution of the 4-MPM-1,2,5,20-tetraol (2.0 mg, 0.0023 mmol) stirred in 0.2 ml of CH_2Cl_2 and 0.02 ml of 2,2-dimethoxypropane at 0 °C was added a solution of *p*-toluenesulfonic acid (0.002 ml, 0.1M in THF, 0.0002 mmol). The resulting solution was stirred for 20 min then triethylamine (0.1 ml) was added and stirring was continued for 10 min. The mixture was rinsed into ethyl acetate (10 ml) over saturated aqueous $NaHCO_3$ then the aqueous phase was extracted with ethyl acetate (2 x 5 ml). The combined extracts were washed with brine, dried with Na_2SO_4, and filtered. Concentration of the filtrate under vacuum yielded 2.1 mg of crude material which was purified by silica gel chromatography to yield 1.1 mg of acetonide **26b**.

26b (P_{520}=$C(CH_3)_2$, P_7=BOM): ^{1}H NMR (500 MHz, $CDCl_3$) δ– 0.073 (s, 3H, TBS CH_3), 0.008 (s, 3H, TBS CH_3), 0.60 (q, J = 7.9Hz, 6H, TES CH_2), 0.79 (s, 9H, TBS t-Bu), 0.95(t, J = 7.9 Hz, 9H, TES CH_3), 1.10 (s, 3H, CH_3 19), 1.25 (s, 3H, CH_3 17), 1.34 (s, 3H, CH_3 16), 1.41 (s, 3H, CH_3 acetonide), 1.46 (s, 3H, CH_3 acetonide), 1.88 (dd, J = 16.7,5.5 Hz, H9β), 2.08 (dd, J = 14.3, 9.2 Hz, 1H, H14β), 2.17 (s, 3H, CH_3 18), 2.21(dd, J = 17.1, 1.7 Hz, 1H,

H9α), 2.42 (dd, J = 14.3,7.2 Hz, 1H, H14α), 2.61 (d, J = 5.1 Hz, 1H, H3α), 2.62 (m, 1H, H6β), 3.71 (dd, J = 11.3, 5.1Hz, 1H, H2β), 3.75 (dd, J = 5.0, 11.3 Hz, 1H, H7α), 3.80 (s, 3H, OCH_3), 3.99 (dd, J =12.0, 6.2 Hz, 1H, H5α), 4.01 (d, J = 14.2 Hz, 1H, H20), 4.17 (s, 1H, OH1), 4.44 (d, J = 14.2 Hz, 1H, H20), 4.47 (d, J = 11.6 Hz, 1H, $OC\underline{H}_2Ph$), 4.58 (m, 1H, H10β), 4.80 (d, J = 11.6 Hz, 1H, $OC\underline{H}_2Ph$), 4.84(d, J = 11.3 Hz, 1H, OH2), 4.85 (m, 1H, H13β), 4.88 (d, J = 10.3 Hz, 1H, OCH_2O), 4.89 (d, J = 6.8 Hz, 1H, MPM $C\underline{H}_2$), 5.00 (d, J = 10.3 Hz, 1H, $OC\underline{H}_2Ph$), 5.10 (d, J = 6.8 Hz, 1H, MPM $C\underline{H}_2$), 6.85 (d, J = 8.9 Hz, 2H, *p*-MeO<u>Ph</u> -*o*), 7.27 (d, J = 8.9 Hz, 2H, *p*-MeO<u>Ph</u> -*m*), 7.27-7.36 (m, 5H, <u>Ph</u>CH_2).

Diolcarbonate **27b**: To a solution of the diol **26b** (P_{520}=$C(CH_3)_2$, P_7=BOM) (1.1 mg) in 0.2 mL of CH_2Cl_2 and 0.02 mL of pyridine stirred at -78 °C was added a solution of phosgene (0.010 mL, 2M in toluene, 0.02 mmol). The resulting solution was stirred at -78 °C for 10 min then warmed to 0 °C for 3 h. The mixture was diluted with 30% ethyl acetate in hexanes (5 mL) then poured into 30% ethyl acetate in hexanes (10 mL) over saturated aqueous $NaHCO_3$. The aqueous phase was extracted with 30% ethyl acetate in hexanes (2 x 5 mL) then the combined extracts were washed with brine, dried with Na_2SO_4, and filtered. Concentration of the filtrate under vacuum yielded 1.3mg of crude material. Purification by silica gel chromatography yielded 0.9 mg of pure 1,2-cyclic carbonate.

To a solution of the carbonate stirred in 0.1 ml of THF and 0.05 mL of methanol was added a solution of pyridinium tosylate (0.005 ml, 0.1M in CH_2Cl_2). The mixture was stirred at room temperature for 24 h and partitioned between saturated sodium bicarbonate and ethyl acetate. The ethyl acetate layer was dried over sodium sulfate and evaporated to give 0.9 mg of diol **27b**.

27b (P_7=BOM): ^{1}H NMR (500 MHz, $CDCl_3$) δ– 0.24 (s, 3H, TBS CH_3), -0.038 (s, 3H, TBS CH_3), 0.58 (q, J = 8.1Hz, 6H, TES CH_2), 0.84 (s, 9H, TBS t-Bu), 0.93(t, J = 8.1 Hz, 9H, TES CH_3),1.14 (s, 3H, CH_3 19), 1.19 (s, 3H, CH_3 17), 1.34 (s, 3H, CH_3 16), 1.88 (br d, J = 17 Hz, H9β), 2.00 (br q, J = 12 Hz, 1H, H6β), 2.08 (d, J = 1.4 Hz, 3H, CH_3 18), 2.2 (m, 2H, H9α and 14β), 2.35 (br s, 1H, H3α), 2.39 (dt, J = 4.8, 13 Hz, H6α), 2.74 (br s, 1H, 20 OH), 2.87 (dd, J = 15.1 ,5.1 Hz, 1H, H14α), 3.71 (dd, J = 11.3, 5.1Hz, 1H, H2β), 3.58 (br s, 2H, H7α and 20 OH), 3.78 (s, 3H, OCH_3), 3.78 (br m, 1H, H5α), 4.37 (dd, J = 13.0, 5.8 Hz, 1H,

H20), 4.39 (dd, J = 4.8, 5.8 Hz, 1H, H10β), 4.47 (m, 2H, H20 and 2β), 4.59 (d, J = 11.6 Hz, 1H, OC<u>H</u>$_2$Ph), 4.63 (br m, 1H, H13β), 4.71 (d, J = 11.6 Hz, 1H, OC<u>H</u>$_2$Ph), 4.88 (d, J = 7.2 Hz, 1H, OCH_2O),4.91 (d, J = 7.2 Hz, 1H, OCH_2O), 4.93 (m, 2H, MPM <u>CH$_2$</u>), 6.84 (d, J = 8.6 Hz, 2H, *p*-MeO<u>Ph</u> -*o*), 7.23 (d, J = 8.6 Hz, 2H, *p*-MeO<u>Ph</u> -*m*), 7.27-7.36 (m, 5H, <u>Ph</u> CH_2).

Mesylate **28b**. To a stirred solution of diol **27b** (0.9 mg) in pyridine (0.6 mL) under nitrogen at 0° C was added dropwise methanesulfonyl chloride (0.02 mL). After 12 h, a saturated aqueous $NaHCO_3$ solution (0.05 mL) was added. The mixture was stirred for 10 min, poured into 20 mL of a saturated aqueous $NaHCO_3$ solution and extracted with 40% ethyl acetate/hexane (20 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 1 mg of **28b** as a colorless oil.

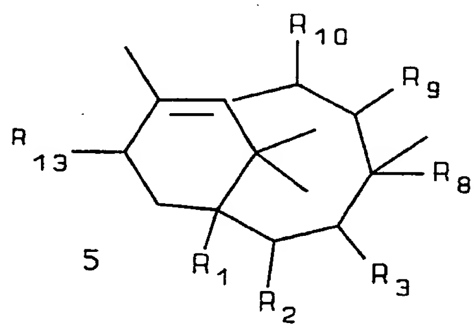
Oxetane 29. To a stirred solution of mesylate **28b** (1 mg) in toluene (0.4 mL) under nitrogen at room temperature was added diisopropyl ethylamine (0.008 mL). The solution was refluxed for 3.5 h, cooled to room temperature, poured into 20 mL of a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (20 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 1.5 mg of a pale yellow oil. The oil was column chromatographed (30% ethyl acetate/hexane) to yield 1 mg of MPM oxetane. This material was dissolved in 1 mL of methylene chloride, 0.1 mL of 0.1 M phosphate buffer and 1 mg of DDQ were added, and the mixture was stirred at ambient temperature for 2h. The mixture was poured into 20 mL of a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (20 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 1.0 mg of an oil. To a stirred solution of this material (1 mg) and dimethyl aminopyridine (1.5 mg) in pyridine (10 μL) under nitrogen at room temperature was added acetic anhydride (5 μL). The solution was stirred for 15 h, diluted with ethyl acetate, poured into 20 mL of a 10% aqueous $CuSO_4$ solution and extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2 mg of a pale yellow oil. The oil was column chromatographed (25% ethyl acetate/hexane) to yield 0.6 mg of oxetane **29**.

In view of the above, it will be seen that the several objects of the invention are achieved.

As various changes could be made in the above compositions without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting sense.

WHAT WE CLAIM IS:

1. An intermediate for use in the preparation of a tricyclic or tetracyclic taxane having the formula:



wherein

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, or together with R_1 is a carbonate;

R_3 is hydrogen, hydroxy, protected hydroxy, $-OCOR_{32}$, or oxo;

R_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl;

R_9 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{33}$, or together with R_{10} is a carbonate;

R_{10} is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{29}$, or together with R_9 is a carbonate;

R_{13} is hydrogen, hydroxy, protected hydroxy, $-OCOR_{35}$ or MO-;

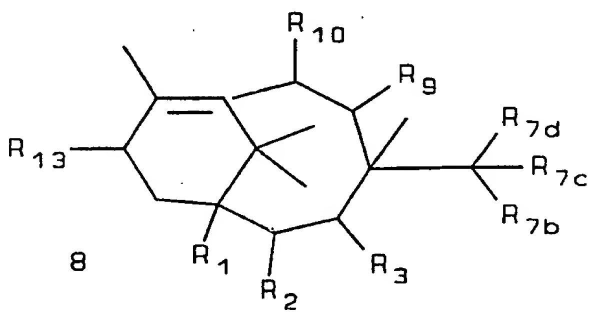
R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, and R_{35} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

M comprises ammonium or is a metal.

2. An intermediate for use in the preparation of a tricyclic or tetracyclic taxane having the formula:



8

wherein

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, or together with R_1 is a carbonate;

R_3 is hydrogen, hydroxy, protected hydroxy, $-OCOR_{32}$, or oxo, or together with R_{7b} is a carbonate;

R_{7b} is hydrogen, alkyl, cyano, hydroxy, protected hydroxy, or $-OCOR_{36}$, or together with R_3 or R_9 is a carbonate;

R_{7c} and R_{7d} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl;

R_9 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{33}$, or together with R_{7b} or R_{10} is a carbonate;

R_{10} is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{29}$, or together with R_9 is a carbonate;

R_{13} is hydrogen, hydroxy, protected hydroxy, $-OCOR_{35}$ or MO-;

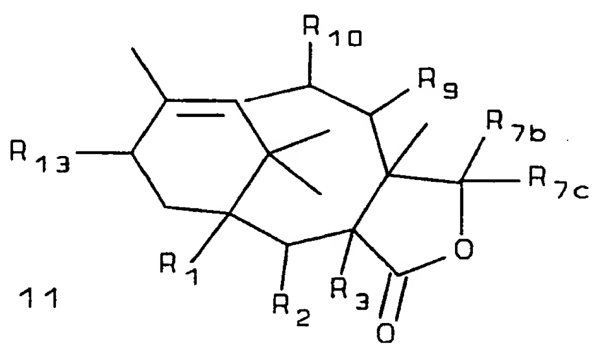
R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{35} and R_{36} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

M comprises ammonium or is a metal.

3. An intermediate for use in the preparation of a tricyclic or tetracyclic taxane having the formula:



11

wherein

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, or together with R_1 is a carbonate;

R_3 is hydrogen, hydroxy, protected hydroxy, or $-OCOR_{32}$;

R_{7c} and R_{7d} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl;

R_9 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{33}$, or together with R_{10} is a carbonate;

R_{10} is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{29}$, or together with R_9 is a carbonate;

R_{13} is hydrogen, hydroxy, protected hydroxy, $-OCOR_{35}$ or MO-;

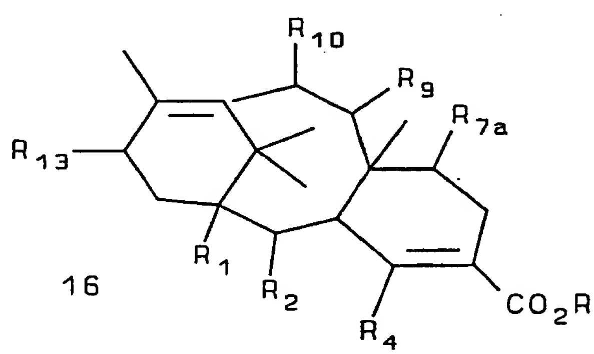
R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, and R_{35} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, -NX_8X_{10}, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

M comprises ammonium or is a metal.

4. An intermediate for use in the preparation of a tricyclic or tetracyclic taxane having the formula:



16

wherein

R is C_1 - C_8 alkyl,

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, together with R_1 is a carbonate, or together with R_{4a} is a carbonate;

R_{4a} is hydrogen, alkyl, hydroxy, protected hydroxy, or $-OCOR_{27}$, or together with R_2 is a carbonate;

R_{7a} is hydrogen, halogen, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{34}$, or together with R_9 is a carbonate;

R_9 is hydrogen, oxo, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{33}$, or together with R_{7a} or R_{10} is a carbonate;

R_{10} is hydrogen, oxo, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{29}$, or together with R_9 is a carbonate;

R_{13} is hydrogen, hydroxy, protected hydroxy, $-OCOR_{35}$ or MO-;

R_{28} is a functional group which increases the solubility of the taxane derivative;

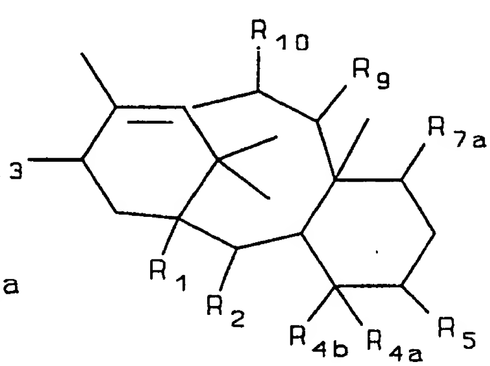
R_{29}, R_{30}, R_{31}, R_{33}, R_{34} and R_{35} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

M comprises ammonium or is a metal.

5. An intermediate for use in the preparation of a tricyclic or tetracyclic taxane having the formula:



26a

wherein

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, or together with R_1 or R_{4a} is a carbonate;

R_{4a} is hydrogen, alkyl, hydroxy, protected hydroxy, or $-OCOR_{27}$, together with R_{4b} is an oxo, or together with R_2, R_{4b}, or R_5 is a carbonate;

R_{4b} is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or cyano, together with R_{4a} is an oxo, together with R_{4a} or R_5 is a carbonate, or together with R_5 and the carbons to which they are attached form an oxetane ring;

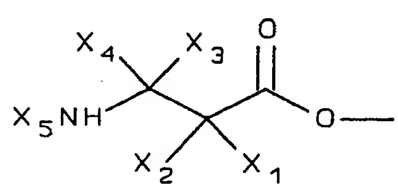
R_5 is hydrogen, hydroxy, protected hydroxy, $-OCOR_{--}$, oxo, together with R_{4a} or R_{4b} is a carbonate, or together with R_{4b} and the carbons to which they are attached form an oxetane ring;

R_{7a} is hydrogen, halogen, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{34}$, or together with R_9 is a carbonate;

R_9 is hydrogen, oxo, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{33}$, or together with R_{7a} or R_{10} is a carbonate;

R_{10} is hydrogen, oxo, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{29}$, or together with R_9 is a carbonate;

R_{13} is hydrogen, hydroxy, protected hydroxy, $-OCOR_{35}$, MO- or



;

R_{28} is a functional group which increases the solubility of the taxane derivative;

R_{27}, R_{29}, R_{30}, R_{31}, R_{33}, R_{34}, and R_{35} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_1 is $-OX_6$, $-SX_7$, or $-NX_8X_9$;

X_2 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_3 and X_4 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_5 is $-COX_{10}$, $-COOX_{10}$, $-COSX_{10}$, $-CONX_8X_{10}$, or $-SO_2X_{11}$;

X_6 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, hydroxy protecting group, or a functional group which increases the water solubility of the taxane derivative;

X_7 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or sulfhydryl protecting group;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_9 is an amino protecting group;

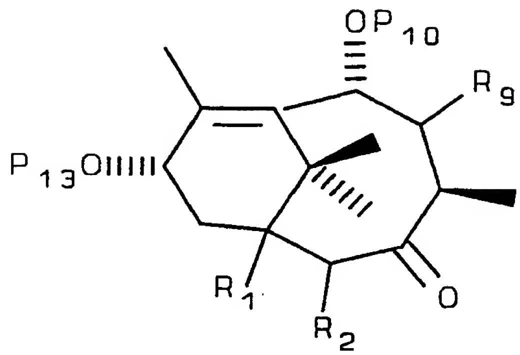
X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_{11} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-OX_{10}$, or $-NX_8X_{14}$;

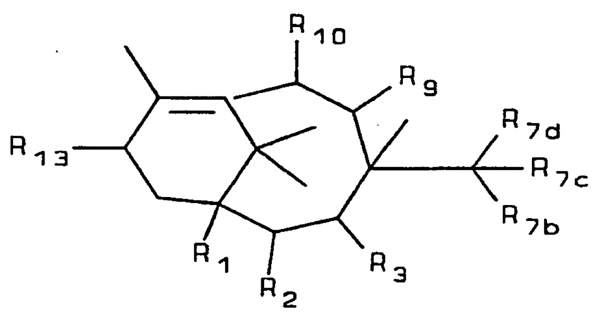
X_{14} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

M comprises ammonium or is a metal.

6. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula



with $BrMgN(iPr)_2$, an aldehyde (or ketone), followed by phosgene and an alcohol to form a compound having the formula:



wherein

R_1 is hydrogen or protected hydroxy; R_2 is hydrogen or protected hydroxy;

R_3 is oxo;

R_{7b} is hydrogen, alkyl, cyano, hydroxy, protected hydroxy, or $-OCOR_{36}$, or together with R_3 or R_9 is a carbonate;

R_{7c} and R_{7d} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl;

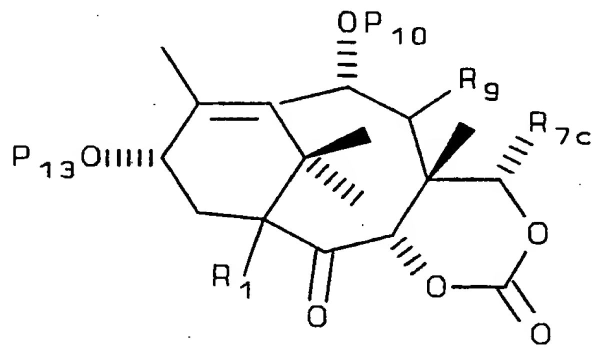
R_9 is hydrogen, protected hydroxy, or oxo;

R_{10} is $-OP_{10}$;

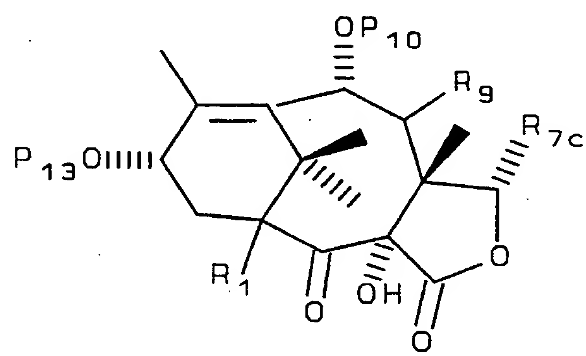
R_{13} is $-OP_{13}$; and

P_{10} and P_{13} are hydroxy protecting groups.

7. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula



with lithium tetramethylpiperidide to form a compound having the formula:



;

wherein

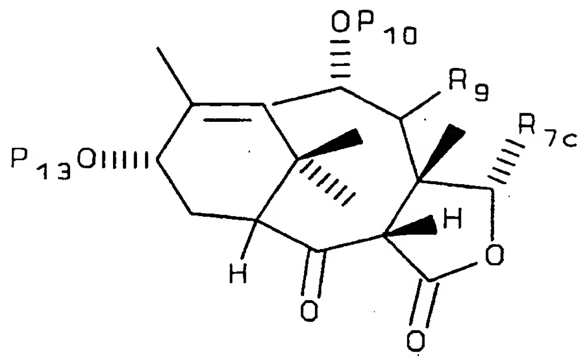
R_1 is hydrogen or protected hydroxy;

R_{7c} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl;

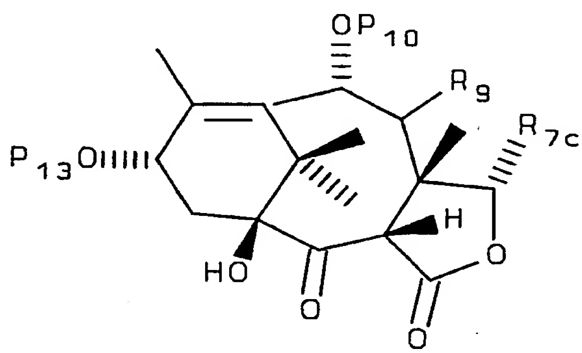
R_9 is hydrogen, protected hydroxy, or oxo; and

P_{10} and P_{13} are hydroxy protecting groups.

8. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula:



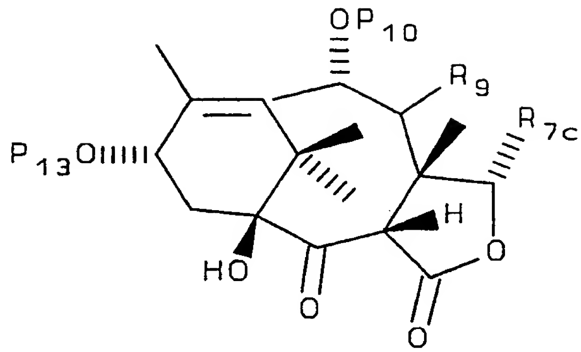
with lithium tetramethylpiperidide and camphosulfonyl oxaziridine to form a compound having the formula:



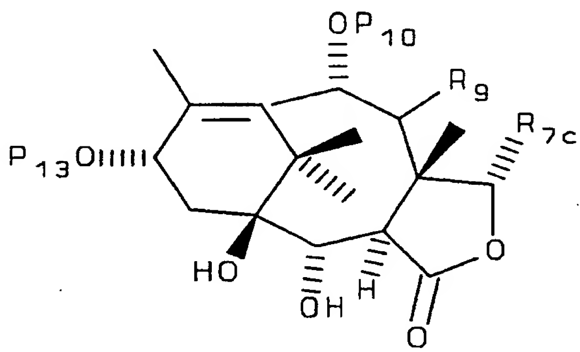
;

wherein R_9 is hydrogen, protected hydroxy, or oxo; R_{7c} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl; and P_{10} and P_{13} are hydroxy protecting groups.

9. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula:



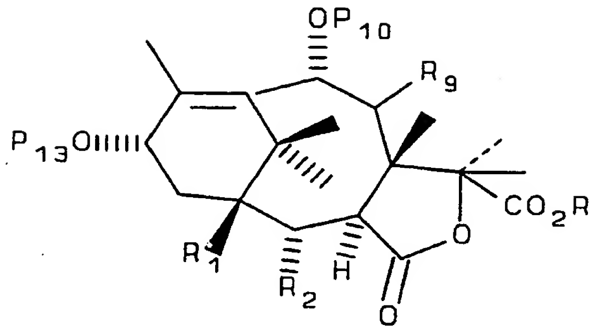
with a hydride reducing agent to form a compound having the formula:



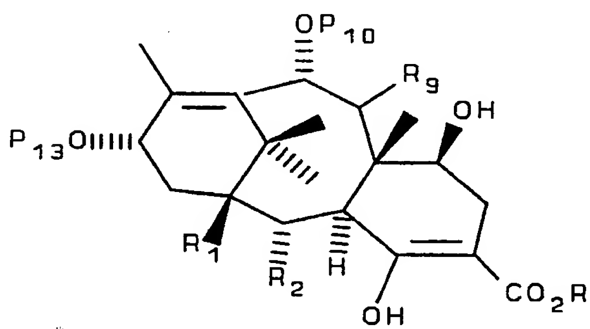
;

wherein R_9 is hydrogen, protected hydroxy, or oxo; R_{7c} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl; and P_{10} and P_{13} are hydroxy protecting groups.

10. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula:



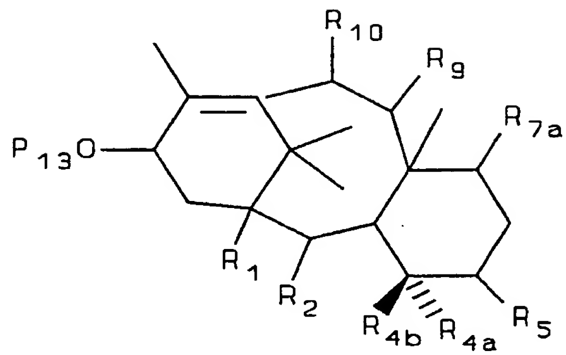
with lithium diisopropylamide to form a compound having the formula:



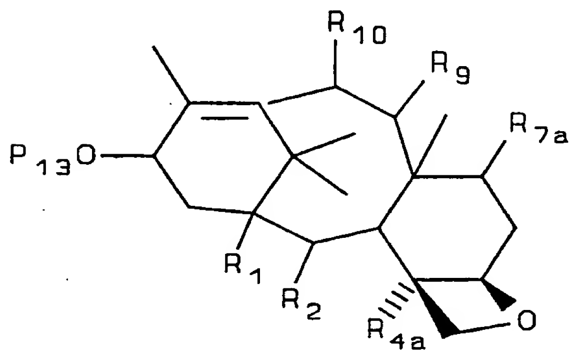
;

wherein R is lower alkyl, R_1 is hydrogen, protected hydroxy or R_1 and R_2 together form a carbonate, R_2 is hydrogen, protected hydroxy or R_1 and R_2 together form a carbonate, R_9 is hydrogen, protected hydroxy, or oxo; R_{7c} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl; and P_{10} and P_{13} are hydroxy protecting groups.

11. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula:



with DBU to form a compound having the formula:



wherein

R_1 is hydrogen, hydroxy, protected hydroxy or -OCOR$_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or -OCOR$_{31}$, or together with R_1 is a carbonate;

R_{4a} is hydrogen, alkyl, hydroxy, or protected hydroxy, or together with R_2 is a carbonate;

R_{4b} is hydroxymethylene;

R_5 is -OMs, -OTs or a bromide;

R_{7a} is hydrogen, protected hydroxy, or -OCOR$_{34}$, or together with R_9 is a carbonate;

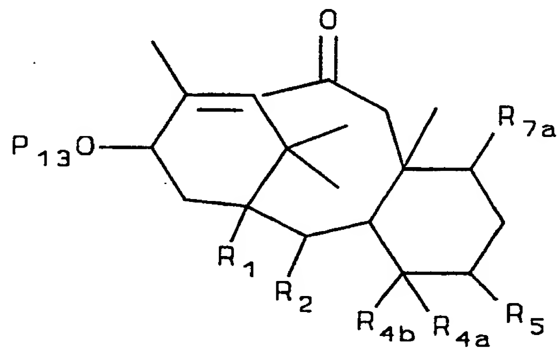
R_9 is hydrogen, oxo, hydroxy, protected hydroxy, or -OCOR$_{33}$, or together with R_{7a} or R_{10} is a carbonate;

R_{10} is hydrogen, oxo, hydroxy, protected hydroxy, or -OCOR$_{29}$, or together with R_9 is a carbonate;

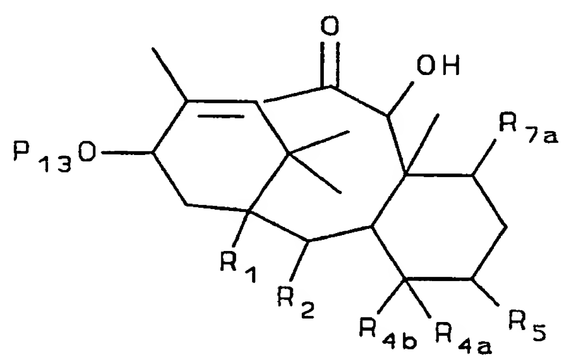
R_{13} is hydrogen, hydroxy, protected hydroxy, or -OCOR$_{35}$;

R_{29}, R_{33}, R_{34} and R_{35} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl.

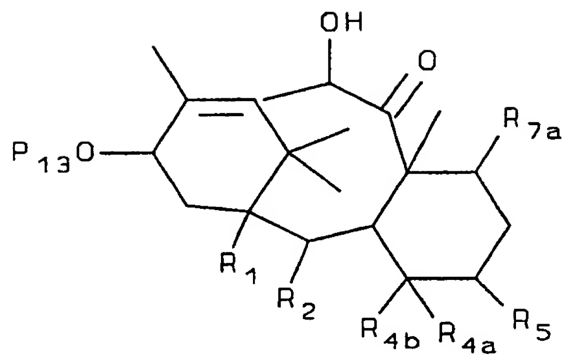
12. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula:



with KOtBu and $(PhSeO)_2O$ to form a reaction product having the formula:



and exposing the reaction product to additional KOtBu, silica gel, or other acids or bases, or to heat to rearrange the reaction product to a compound having the formula:



wherein

R_1 is hydrogen, hydroxy, protected hydroxy, or together with R_2 is a carbonate;

R_2 is hydrogen, protected hydroxy, or $-OCOR_{31}$, or together with R_1 or R_{4a} is a carbonate;

R_{4a} is hydrogen, alkyl, hydroxy, protected hydroxy, or $-OCOR_{27}$, together with R_{4b} is an oxo, or together with R_2, R_{4b}, or R_5 is a carbonate;

R_{4b} is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or cyano, together with R_{4a} is an oxo, together with R_{4a} or R_5 is a carbonate, or together with R_5 and the carbons to which they are attached form an oxetane ring;

R_5 is hydrogen, protected hydroxy, $-OCOR_{37}$, together with R_{4a} or R_{4b} is a carbonate, or together with R_{4b} and the carbons to which they are attached form an oxetane ring;

R_{7a} is hydrogen, halogen, protected hydroxy, or $-OCOR_{34}$; and

R_{27}, R_{29}, R_{30}, R_{31}, R_{33}, R_{34}, R_{35} and R_{37} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl; and

X_{10} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterosubstituted alkyl, alkenyl alkynyl, aryl or heteroaryl.

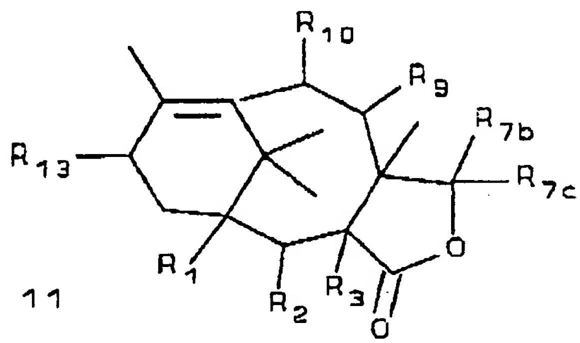
AMENDED CLAIMS

[received by the International Bureau on 6 January 1995 (06.01.95); original claims 3,4,5,11 and 12 amended; other claims unchanged (14 pages)]

X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

M comprises ammonium or is a metal.

3. An intermediate for use in the preparation of a tricyclic or tetracyclic taxane having the formula:



11

wherein

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, or together with R_1 is a carbonate;

R_3 is hydrogen, hydroxy, protected hydroxy, or $-OCOR_{32}$;

R_{7b} is hydrogen, alkyl, cyano, hydroxy, protected hydroxy, or $-OCOR_{36}$, or together with R_3 or R_9 is a carbonate;

R_{7c} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl;

R_9 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{33}$, or together with R_{10} is a carbonate;

R_{10} is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{29}$, or together with R_9 is a carbonate;

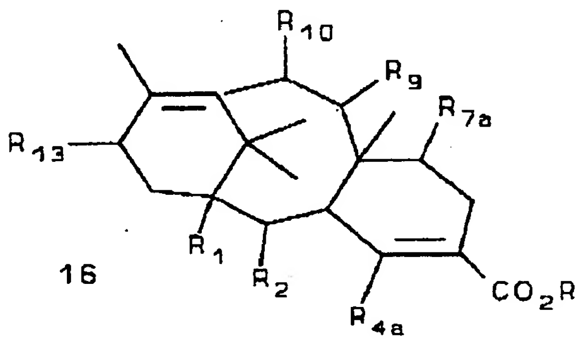
R_{13} is hydrogen, hydroxy, protected hydroxy, $-OCOR_{25}$ or MO-;

R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{35}, and R_{36} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, -NX_8X_{10}, -SX_{10}, monocyclic aryl or monocyclic heteroaryl;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and M comprises ammonium or is a metal.

4. An intermediate for use in the preparation of a tricyclic or tetracyclic taxane having the formula:



16

wherein

R is C_1 - C_8 alkyl,

R_1 is hydrogen, hydroxy, protected hydroxy or -$OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or -$OCOR_{31}$, together with R_1 is a carbonate, or together with R_{4a} is a carbonate;

R_{4a} is hydrogen, alkyl, hydroxy, protected hydroxy, or -$OCOR_{27}$, or together with R_2 is a carbonate;

R_{7a} is hydrogen, halogen, hydroxy, protected hydroxy, -OR_{28}, or -$OCOR_{34}$, or together with R_9 is a carbonate;

R_9 is hydrogen, oxo, hydroxy, protected hydroxy, -OR_{28}, or -$OCOR_{33}$, or together with R_{7a} or R_{10} is a carbonate;

R_{10} is hydrogen, oxo, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{29}$, or together with R_9 is a carbonate;

R_{13} is hydrogen, hydroxy, protected hydroxy, $-OCOR_{35}$ or MO-;

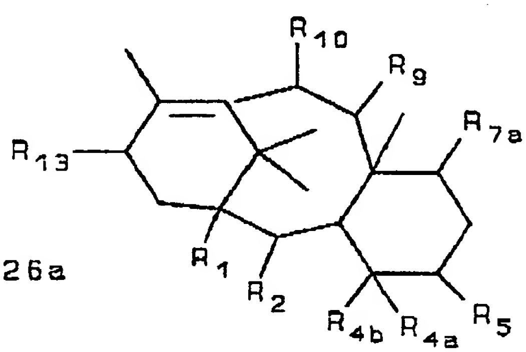
R_{28} is a functional group which increases the solubility of the taxane derivative;

R_{27}, R_{29}, R_{30}, R_{31}, R_{33}, R_{34} and R_{35} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and M comprises ammonium or is a metal.

5. An intermediate for use in the preparation of a tricyclic or tetracyclic taxane having the formula:



26a

wherein

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, or together with R_1 or R_{4a} is a carbonate;

R_{4a} is hydrogen, alkyl, hydroxy, protected hydroxy, or $-OCOR_{27}$, together with R_{4b} is an oxo, or together with R_2, R_{4b}, or R_5 is a carbonate;

R_{4b} is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or cyano, together with R_{4a} is an oxo, together with R_{4a} or R_5 is a carbonate, or together with R_5 and the carbons to which they are attached form an oxetane ring;

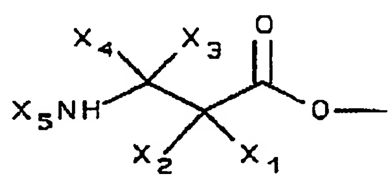
R_5 is hydrogen, hydroxy, protected hydroxy, $-OCOR_{[illegible]}$, oxo, together with R_{4a} or R_{4b} is a carbonate, or together with R_{4b} and the carbons to which they are attached form an oxetane ring;

R_{7a} is hydrogen, halogen, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{34}$, or together with R_9 is a carbonate;

R_9 is hydrogen, oxo, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{33}$, or together with R_{7a} or R_{10} is a carbonate;

R_{10} is hydrogen, oxo, hydroxy, protected hydroxy, $-OR_{28}$, or $-OCOR_{29}$, or together with R_9 is a carbonate;

R_{13} is hydrogen, hydroxy, protected hydroxy, $-OCOR_{35}$, MO- or



;

R_{26} is a functional group which increases the solubility of the taxane derivative;

R_{27}, R_{29}, R_{30}, R_{31}, R_{33}, R_{34}, and R_{35} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_1 is $-OX_6$, $-SX_7$, or $-NX_8X_9$;

X_2 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_3 and X_4 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_5 is $-COX_{10}$, $-COOX_{10}$, $-COSX_{10}$, $-CONX_8X_{10}$,

or $-SO_2X_{11}$;

X_6 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, hydroxy protecting group, or a functional group which increases the water solubility of the taxane derivative;

X_7 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or sulfhydryl protecting group;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_9 is an amino protecting group;

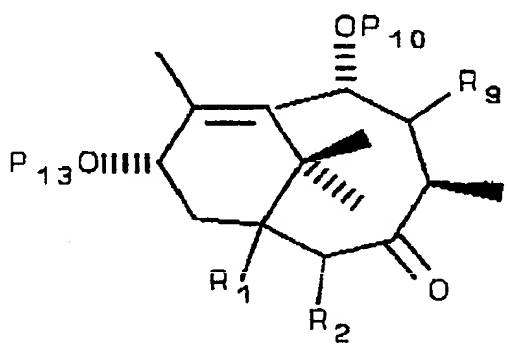
X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_{11} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-OX_{10}$, or $-NX_8X_{14}$;

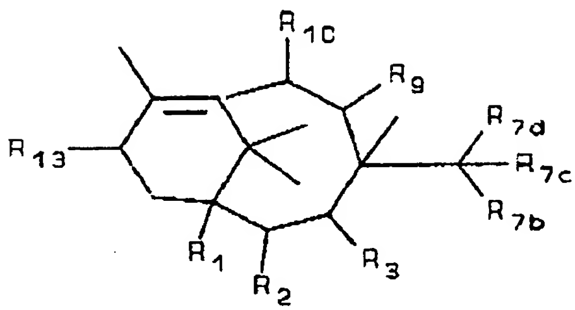
X_{14} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

M comprises ammonium or is a metal.

6. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula



with $BrMgN(iPr)_2$, an aldehyde (or ketone), followed by phosgene and an alcohol to form a compound having the formula:



wherein

R_1 is hydrogen or protected hydroxy; R_2 is hydrogen or protected hydroxy;

R_3 is oxo;

R_{7b} is hydrogen, alkyl, cyano, hydroxy, protected hydroxy, or $-OCOR_{36}$;

R_{7c} and R_{7d} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl;

R_9 is hydrogen, protected hydroxy, or oxo;

R_{10} is $-OP_{10}$;

R_{13} is $-OP_{13}$;

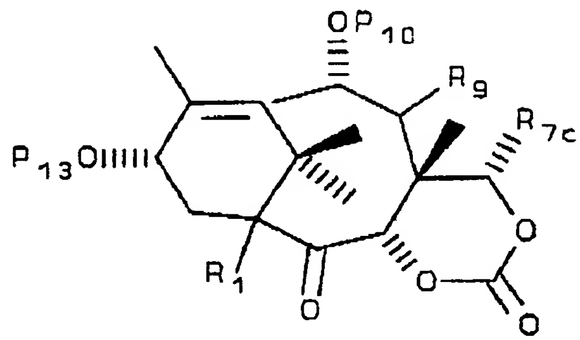
R_{36} is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

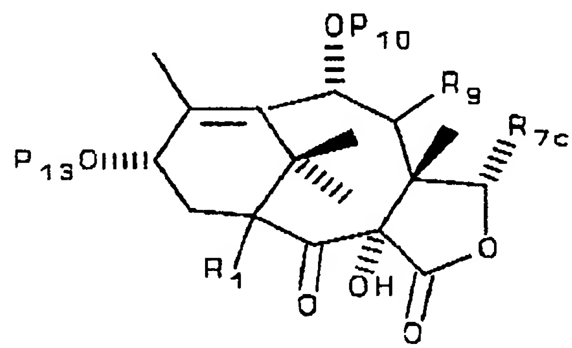
X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

P_{10} and P_{13} are hydroxy protecting groups.

7. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula



with lithium tetramethylpiperidide to form a compound having the formula:



;

wherein

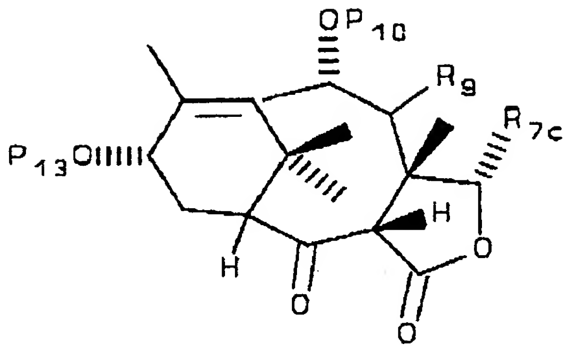
R_1 is hydrogen or protected hydroxy;

R_{7c} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl;

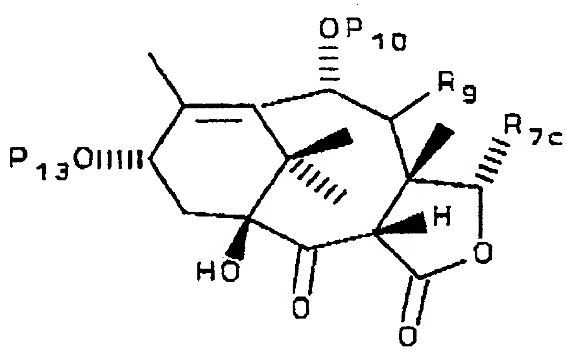
R_9 is hydrogen, protected hydroxy, or oxo; and

P_{10} and P_{13} are hydroxy protecting groups.

8. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula:



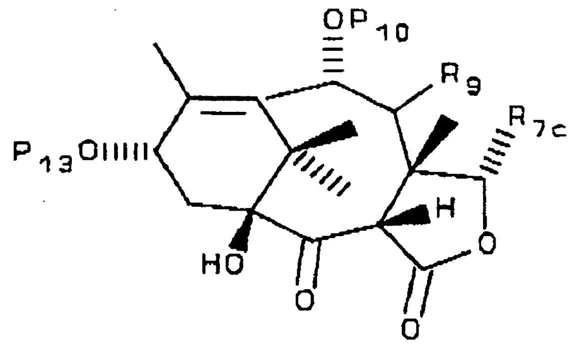
with lithium tetramethylpiperidide and camphosulfonyl oxaziridine to form a compound having the formula:



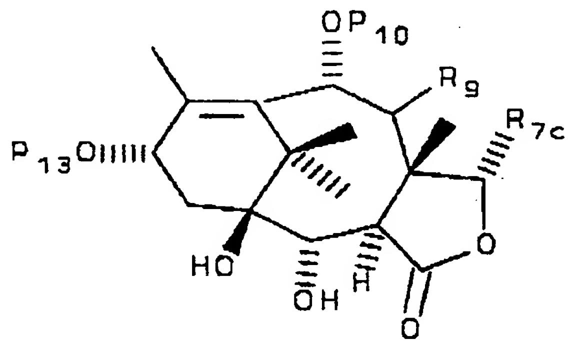
;

wherein R_9 is hydrogen, protected hydroxy, or oxo; R_{7c} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl; and P_{10} and P_{13} are hydroxy protecting groups.

9. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula:



with a hydride reducing agent to form a compound having the formula:

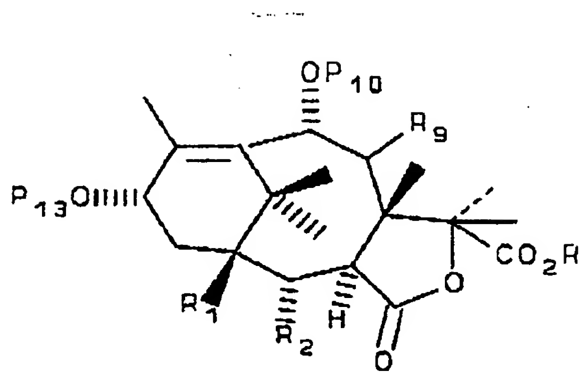


;

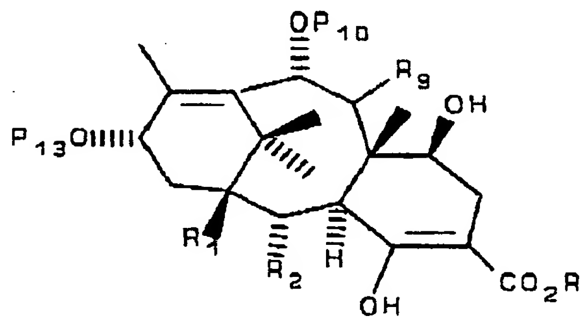
wherein R_9 is hydrogen, protected hydroxy, or oxo; R_{7c} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl; and P_{10} and P_{13} are hydroxy protecting groups.

10. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula:

AMENDED SHEET (ARTICLE 19)



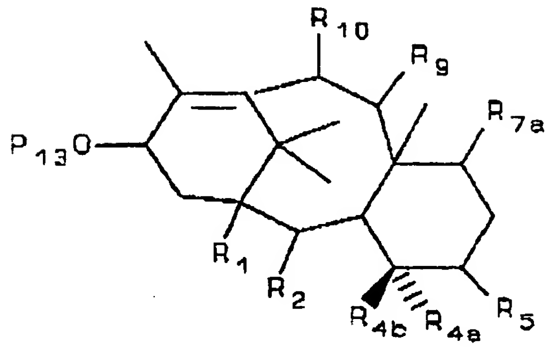
with lithium diisopropylamide to form a compound having the formula:



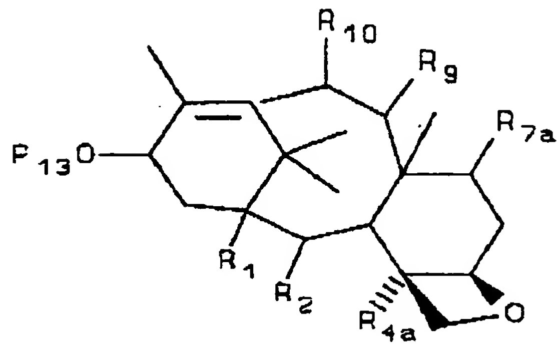
;

wherein R is lower alkyl, R_1 is hydrogen, protected hydroxy or R_1 and R_2 together form a carbonate, R_2 is hydrogen, protected hydroxy or R_1 and R_2 together form a carbonate, R_9 is hydrogen, protected hydroxy, or oxo; R_{7a} is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl; and P_{10} and P_{13} are hydroxy protecting groups.

11. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula:



with DBU to form a compound having the formula:



wherein

R_1 is hydrogen, hydroxy, protected hydroxy or $-OCOR_{30}$, or together with R_2 is a carbonate;

R_2 is hydrogen, hydroxy, protected hydroxy, oxo, or $-OCOR_{31}$, or together with R_1 is a carbonate;

R_{4a} is hydrogen, alkyl, hydroxy, or protected hydroxy, or together with R_2 is a carbonate;

R_{4b} is hydroxymethylene;

R_5 is -OMs, -OTs or a bromide;

R_{7a} is hydrogen, protected hydroxy, or $-OCOR_{34}$, or together with R_9 is a carbonate;

R_9 is hydrogen, oxo, hydroxy, protected hydroxy, or $-OCOR_{33}$, or together with R_{7a} or R_{10} is a carbonate;

R_{10} is hydrogen, oxo, hydroxy, protected hydroxy, or $-OCOR_{29}$, or together with R_9 is a carbonate;

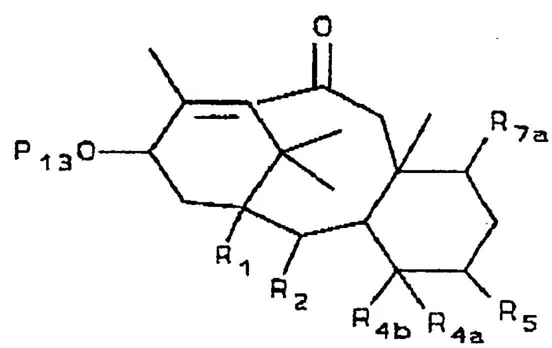
P_{13} is a hydroxy protecting group;

R_{29}, R_{30}, R_{31}, R_{33}, and R_{34} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

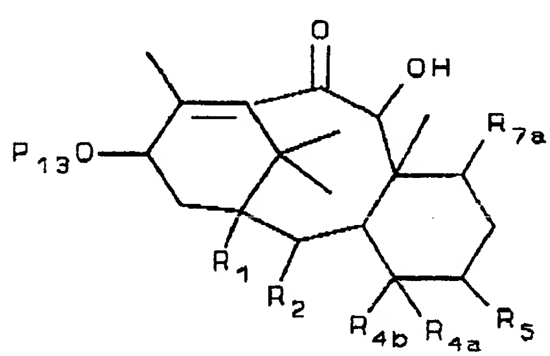
X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl; and

X_{10} is alkyl, alkenyl, alkynyl, aryl, or heteroaryl.

12. A process for the preparation of an intermediate useful in the synthesis of a tricyclic or tetracyclic taxane comprising reacting a compound having the formula:

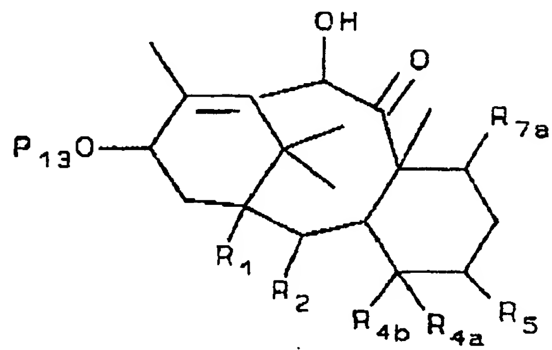


with KOtBu and $(PhSeO)_2O$ to form a reaction product having the formula:



and exposing the reaction product to additional KOtBu, silica gel, or other acids or bases, or to heat to

rearrange the reaction product to a compound having the formula:



wherein

R_1 is hydrogen, hydroxy, protected hydroxy, or together with R_2 is a carbonate;

R_2 is hydrogen, protected hydroxy, or $-OCOR_{31}$, or together with R_1 or R_{4a} is a carbonate;

R_{4a} is hydrogen, alkyl, hydroxy, protected hydroxy, or $-OCOR_{27}$, together with R_{4b} is an oxo, or together with R_2, R_{4b}, or R_5 is a carbonate;

R_{4b} is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or cyano, together with R_{4a} is an oxo, together with R_{4a} or R_5 is a carbonate, or together with R_5 and the carbons to which they are attached form an oxetane ring;

R_5 is hydrogen, protected hydroxy, $-OCOR_{37}$, together with R_{4a} or R_{4b} is a carbonate, or together with R_{4b} and the carbons to which they are attached form an oxetane ring;

R_{7a} is hydrogen, halogen, protected hydroxy, or $-OCOR_{34}$;

P_{13} is a hydroxy protecting group;

R_{27}, R_{31}, R_{34}, and R_{37} are independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, $-NX_8X_{10}$, $-SX_{10}$, monocyclic aryl or monocyclic heteroaryl;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl; and

X_{10} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterosubstituted alkyl, alkenyl alkynyl, aryl or heteroaryl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/08350

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to Internati nal Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum docum ntation searched (classification system followed by classification symbols)

U.S. : 549/229, 300, 510;
568/347, 375

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

none

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF CHEMICAL SOCIETY, CHEMICAL COMMUNICATION, No. 16, issued August 1992. K.C. Nicolaou et al., "A convergent strategy toward taxol. A facile enantioselective entry into a fully functionalized ring A system", pages 1117-1120.	1-12
X, P	JOURNAL OF AMERICAN CHEMICAL SOCIETY, Volume 116, No. 4, issued 1994, Robert A. Holton et al., "First Total Synthesis of Taxol. 1. Functionalization of the B ring", pages 1597-1598, entire document.	1-12
X, P	JOURNAL OF AMERICAN CHEMICAL SOCIETY, Volume 116, No. 4, issued 1994, Robert A. Holton et al., "First Total Synthesis of Taxol. 2. Completion of the C and D Rings", pages 1599-1600, entire document.	1-12

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 OCTOBER 1994	NOV 07 1994

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	BA TRINH
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/08350

Box I Observations where certain claims were found unsearchabl (C ntinuation f item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07C 45/27, 49/21, 49/203; C07D 305/14, 307/93, 317/70

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :
549/229, 300, 510; 568/347, 375

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I.Claims 1, 2 and 6, drawn to a bicyclic ketone compound and a process of making the same, classified in Class 568, subclasses 347 and 375.

II.Claim 3, drawn to a tricyclic lactone, and classified in Class 549, subclass 300.

III.Claim 7, drawn to a process of making tricyclic lactone, classified in Class 549/300.

IV.Claims 4, 5 and 10, drawn to a tetracyclic carbonate, classified in Class 549, subclass 229.

V.Claim 8, drawn to a process of making tricyclic lactone, classified in Class 549, subclass 300.

VI.Claim 9, drawn to a process of making tricyclic lactone, classified in Class 549, subclass 300.

VII.Claim 11, drawn to a process of making oxetane, classified in Class 549, subclass 510.

VIII.Claim 12, drawn to a process of making tricyclic ketone, classified in Class 568, subclass 347.

The above delineated groups are distinct because the compounds lack a common core structure and are made by different processes using different reaction conditions and reagents. A search of one compound is not required for the other compound, and vice verse. The processes are distinct because of different starting materials being used to make different final products wherein different reaction conditions and reagents have been used. One process would not suggest and/or render the other prima facie obvious in the absence of secondary teachings. 37 CFR 1.475(d).